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## December, 1951

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# BULLETIN
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# OBSERVATIONS ON SOME POSSIBLE PRECURSORS OF ESSENTIAL HYPERTENSION AND CORONARY ARTERY DISEASE*†

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Received for publication August 16, 1951

Essential hypertension and coronary artery disease are extremely prevalent disorders which are so intertwined that study of one requires clear comprehension of the other. Approximately 40% of persons over the age of 50 suffer from hypertension. Coronary artery disease is preceded by hypertension in from 55% to 80% of cases (1, 2). These diseases are by no means confined to old age; they may occur disastrously in early middle life. While the exact time of onset is usually difficult to establish, the disease process is often well advanced before symptoms bring the patient to the doctor. In regard to essential hypertension, the diagnosis was first made at an average age of 36 years in Perera's study of 2,147 patients. The age at which elevation of pressure began was before the age of 40 in 92% of 200 subjects, and under the age of 48 in the remainder (3). Coronary artery disease may also begin early. Eight hundred and sixty-six instances of myocardial infarction in soldiers 18 to 39 years of age were described by Yater and his colleagues, and they also discussed 744 civilian cases in the same age group which they had collected from the literature (4). The first attack of myocardial infarction occurred before the age of 60 in over half the 572 cases of Mintz and Katz; 24% of men and 9% of women had their first attack between the ages of 30 and 49 years (5).

On this occasion, I should like to describe a new approach to the understanding of these two disorders. Experience with young hypertensive and coronary patients indicates that many characteristic traits were present and might have been identified long before the onset of clinical disease. We have, therefore, embarked upon an inquiry into the significance of human variation in terms of the future development of hypertension or coronary artery disease. Our purpose is to study the occurrence, nature and interrelationship of such physiologic and psychologic traits in normal young adults, with Johns Hopkins medical students as our subjects, and by follow-up studies to determine which traits are most frequently associated with the early onset of disease. Our

* Read as the Second Alpha Epsilon Iota Lecture at the Medical College of Virginia May 4, 1951.

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investigation is based upon the hypothesis that essential hypertension and coronary artery disease are closely related disorders in which multiple etiological factors play a determining role. The exact form of disease and age of onset in a given individual is thought to depend on the nature and number of the factors in his own genetic inheritance, in combination with the severity of the stresses encountered as he goes through life. Medical students were chosen as subjects because they are intelligent, efficiently functioning young adults, at an age when growth is virtually complete and degenerative changes are at a minimum. The family incidence of disease may be determined in this group with unusual accuracy. Also, the prevalence of coronary disease among physicians should prove a valuable aid in the long-term interpretation of our findings. Our subjects are available for intensive study for four academic years, and may always be reached for follow-up information after graduation through medical directories. Data obtained include detailed hereditary studies; studies of the cardiovascular system at rest and under stress (cold pressor test, exercise test, controlled anoxemia test); studies of metabolic patterns (diet, nutrition, blood cholesterol, circulating eosinophils, acute sodium withdrawal) and studies of personality (habit survey, family data, Rorschach test). Today I shall present a brief panorama composed of glimpses at various phases of the study.

First, let me show some examples of the way our unselected population may be sorted into various graded series useful for purposes of cross-correlation. Granted that none of these differentiations are perfect or absolute; nevertheless, in general the individuals at one end of a given spectrum do differ significantly from those at the other end in regard to the factor under analysis.

## I. HEREDITARY FACTOR

There are many reports of apoplexy, hypertension and heart attacks running in families. Platt concluded that "the evidence is compatible with the hypothesis that essential hypertension is a hereditary disease conveyed as a Mendelian dominant, with a rate of expression of more than 90 per cent" (6). Hypertension and coronary artery disease are often found in different members of the same family as well as in the same individual.

We have sought detailed information concerning the occurrence of these two conditions, as well as diabetes mellitus and obesity, among the grandparents, parents, aunts, uncles and siblings of our subjects, with special attention to age of onset and clinical characteristics of the disease process. Many students have recorded the actual blood pressure readings of their relatives. The spectrum provided by the parental history is as follows (Table I):

A. Among 353 subjects whose parental history is known, 93, or 26%, had at least one parent with hypertension or coronary artery disease.

B. Before graduating from medical school, nearly 8% of the students have had one parent die from these diseases. Nearly half died before the age of 50.

C. Another 7% have a living parent with severe disease, as indicated by a history of stroke, coronary occlusion or heart failure.

D. 11% of the students have a parent with moderate or mild disease, including angina pectoris and the less severe forms of hypertension.

Thus in each class of 75 there are approximately 20 students with known parental history of hypertension or coronary disease. In addition, there are five students in whose parents these diagnoses are probable, but not established, and five or six more with a diabetic or obese parent without known cardiovascular disease. Some subjects cannot determine their parental history accurately, because of divorce, early death from other causes, and so on. No more than half of each class can give a clearcut statement that both parents are thus far free from these four closely related disorders.

TABLE I

*Parental Hypertension and/or Coronary Disease Among 353 Johns Hopkins Medical Students*

| STUDENTS REPORTING: | NO. | % |
|---|---|---|
| A parent's death from these causes | 27 | 7.6 |
| A parent with severe disease (stroke, coronary occlusion, heart failure) | 26 | 7.4 |
| A parent with moderate disease (angina pectoris, enlarged heart, etc.) | 16 | 4.5 |
| A parent with mild hypertension | 24 | 6.8 |
| Total with positive parental history | 93 | 26.3 |

## II. THE FACTORS OF HIGH RESTING BLOOD PRESSURE LEVELS AND HIGH RESTING HEART RATE

Of many studies concerned with "normal blood pressure," two may be cited which arrive at supplementary conclusions on statistically significant groups of subjects. Robinson and Brucer, after studying the range of normal blood pressure in 11,383 persons, concluded that "hypertension heart disease starts during youth and its diagnostic sign is a persistent elevation of blood pressure into levels over 120 systolic and 80 diastolic; frequent intermittent excursions above those levels denote incipient hypertension." They suggest that the genesis of hypertension will show itself in transient elevation of pressure and an ever increasing number of temporary excursions into higher levels. Blood pressure, in their opinion, must be interpreted as a *range* of systolic and a *range* of diastolic pressure; if 120 is the lowest systolic pressure recorded, the subject is hypertensive, while if the highest he is normal. They found that when blood pressure was above 120/80 the mortality rate rose abruptly (7).

Levy, White, Stroud and Hillman studied the annual medical records of 22,741 Army Officers in order to appraise the significance of transient hypertension (8). Blood pressure readings over 150 mm. mercury systolic or over 90 diastolic were considered abnormally high. At all ages, sustained hypertension developed more frequently in those with previous transient hypertension than in those who had never showed an elevation of blood pressure. The rate for disability retirement with cardiovascular renal disease and the death rate from the same cause were both higher in those with previous transient hypertension. From these two studies, it would appear that resting blood pressure levels over 120/80 or transitory rises in blood pressure above 150/90 or both, indicate increased likelihood of permanent hypertension and increased mortality from cardiovascular renal disease. Not only were Army Officers who previously had shown transitory elevation of blood pressure found to have subsequent hypertension more frequently, but, similarly, those who at one time had been noted to have a heart rate of over 100. If *both* transitory hypertension and transitory tachycardia had been observed in the *same* individual, the likelihood of his developing hypertension was considerably greater than if either of these factors had been present singly (9).

With these considerations in mind, examination of the distribution curves shown in Figure 1 reveals that 23.2% of our subjects have a resting systolic pressure of 120 mm. or more and 10.6% have a resting diastolic pressure of 80 mm. or above. Under the conditions of our examination, none showed a heart rate of 100 or more at rest, but transitory tachycardia was sometimes observed during "casual" readings. Our distribution curves are quite similar to those reported for other groups of young adults (10, 11).

### III. CHOLESTEROL FACTOR

The prevalence of atherosclerosis in coronary artery disease has long been established. Evidence is accumulating that coronary atherosclerotic lesions may occur in young individuals, especially males, and are not necessarily proportional to chronological age (4). While arteriolosclerosis of renal arteries is usually a late manifestation of hypertensive disease, atherosclerotic placques in the renal artery itself may at times initiate hypertension (12).

Whether the cholesterol present in early atheromatous lesions is derived from dietary sources or is endogenously synthesized is still uncertain. Atherosclerosis may be produced by feeding high cholesterol diets to rabbits and chickens, and, when combined with thiouracil, to dogs (13, 14). The nature of the derangement of cholesterol metabolism contributing to human atherosclerosis is obscure, largely because adequate diagnostic methods are still lacking. While total blood cholesterol is not uniformly elevated in patients who have suffered from myocardial infarction, high mean cholesterol values in patients with coronary artery disease have frequently been described. Thus

repeated cholesterol determinations on each of 15 patients with previous myocardial infarction or angina pectoris averaged 355 mgms.% in contrast to a mean value of 255 mgms.% for 15 control patients similarly studied (15).

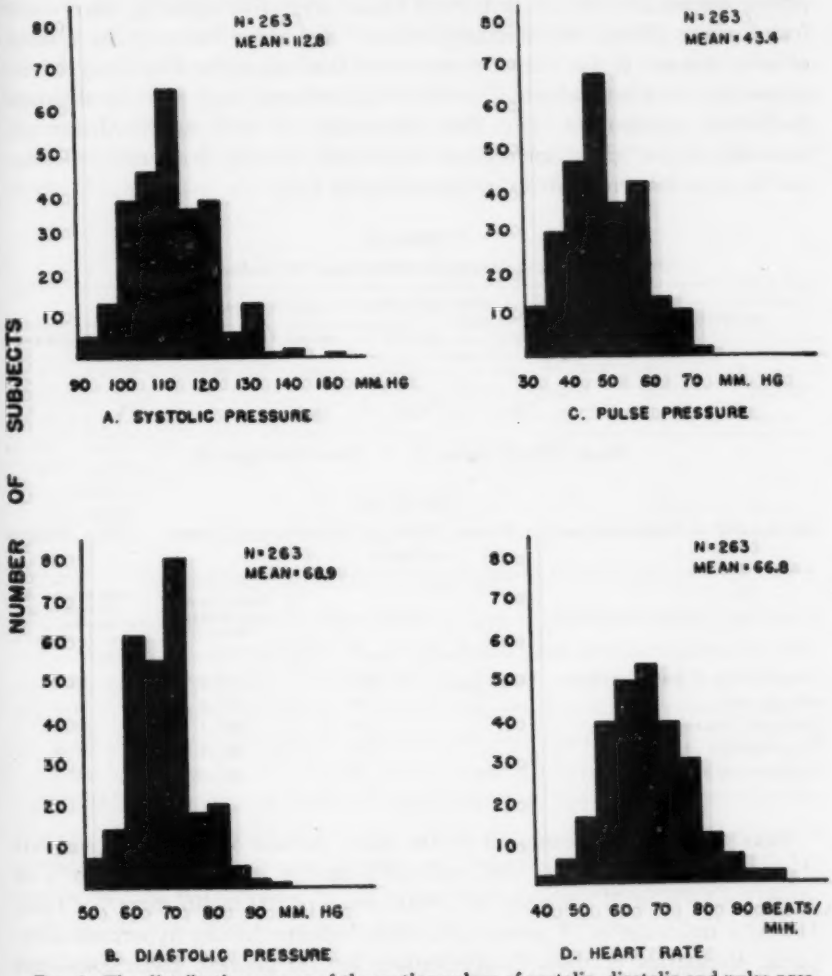


FIG. 1. The distribution curves of the resting values of systolic, diastolic and pulse pressures and of heart rate of all subjects.

In another report, 80% of 28 patients under the age of 40 with coronary disease had blood cholesterol values between 250 and 480 mgms.% (16).

Thus coronary artery disease is often accompanied by high blood cholesterol levels. Conversely, in conditions such as diabetes mellitus in which blood

cholesterol levels are frequently high, atherosclerosis is unusually prevalent at an early age. Of particular interest in this regard is the condition known as "familial hypercholesterolemia." Among patients under 50 with coronary artery disease and serum cholesterol values over 300 mgms.%, many were found whose siblings had similarly elevated cholesterol values in the absence of heart disease. It was therefore concluded that one of the hereditary factors responsible for arteriosclerotic (coronary) heart disease may reside in abnormal cholesterol metabolism (17). The relationship of such an hereditary abnormality to the "giant" molecules of lipoprotein recently described by Gofman and his associates remains to be demonstrated (18).

TABLE II

*Frequency Table of Cholesterol Levels among 332 Medical Students*

| SUBJECTS | BLOOD CHOLESTEROL IN MGMS. % (BLOOR METHOD) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 100–149 | 150–199 | 200–249 | 250–299 | 300–349 | 350–399 | 400–449 |
| No. | 6 | 65 | 141 | 89 | 25 | 5 | 1 |
| % | 1.8 | 19.6 | 42.5 | 26.8 | 7.5 | 1.5 | 0.3 |

Range: 108–407 mgms. % Mean: 234 mgms. %

TABLE III

*Relationship of Cholesterol Level to Parental History of Hypertension, Coronary Disease, Diabetes or Obesity*

| PARENTAL HISTORY | NO. OF SUBJECTS | MEAN BLOOD CHOLESTEROL MGMS. % | PERCENTAGE OF SUBJECTS WITH CHOLESTEROL OF 270 MGMS. % OR ABOVE |
|---|---|---|---|
| Negative for all four disorders | 167 | 229.8 | 16.8 |
| Obesity only | 33 | 231.9 | 12.1 |
| Coronary disease only | 19 | 247.1 | 31.6 |
| Hypertension only | 39 | 247.4 | 30.8 |
| Diabetes only | 8 | 261.6 | 50.0 |

Blood cholesterols determined by the Bloor method on 332 of our subjects show a wide range of variation, with 36% having levels of 250 mgm.% or above, and 9% or 21 students with blood levels of 300 to 407 mgm.% (Table II). At a mean age of 25 years, such levels indicate definite hypercholesterolemia. Repetition of these determinations has, in general, given consistent results. The mean blood cholesterol of students with parental hypertension, coronary disease or diabetes is substantially higher than that of subjects whose parents had no such disorders (Table III). Fifty per cent of subjects with a diabetic parent and 30% of subjects with a hypertensive or coronary parent have blood cholesterol levels of 270 mgm.% or above, in contrast to 17% of subjects whose parents are free from these disorders.

We have analysed blood samples from 10 subjects with high blood cholesterols (mean = 329 mgm.%) by the electrophoretic technique, and compared them with samples from a group of 9 subjects with low blood cholesterols (mean = 171 mgm.%) (Table IV). The most significant difference between the two groups resides in the size of the beta globulin fraction where there is almost no overlapping of their percentage ranges. Differences in the other fractions are less consistent and less striking. These findings suggest that the lipoprotein linkage of bound cholesterol in healthy young adults with hypercholesterolemia is in no way distinctive, since cholesterol is usually contained in the beta globulin, although sometimes in the alpha fraction.*

TABLE IV

*Electrophoretic Analysis*

| | HIGH BLOOD CHOLESTEROL (10 SUBJECTS) | | LOW BLOOD CHOLESTEROL (9 SUBJECTS) | |
|---|---|---|---|---|
| | Mean | Range | Mean | Range |
| Cholesterol mgms. % | 329.4 | 272–410 | 171.0 | 128–200 |
| Albumen % | 53.9 | 51–58 | 60.8 | 53–66 |
| Alpha 1 globulin % | 6.3 | 5–8 | 5.0 | 4–7 |
| Alpha 2 globulin % | 11.7 | 9–14 | 8.9 | 7–13 |
| Beta globulin % | 15.2 | 13–18 | 11.3 | 9–14 |
| Gamma globulin % | 12.9 | 9–16 | 13.6 | 11–16 |

## IV. FACTOR OF CIRCULATORY RESPONSE TO STRESS

The extraordinary lability of blood pressure in patients with hypertension is well recognized. Pressor stimuli include pain, emotional disturbances, exertion and cold (19, 20, 21). Patients with incipient coronary artery disease, on the other hand, tend to show a decreased cardiac output at rest as recorded on the ballistocardiograph (22). We have studied the circulatory response of our subjects to stress by several standardized methods. Physiological stress tests include an oximeter-controlled anoxemia test, during which subjects are studied at different levels of arterial oxygen saturation (23). Subjects inhale a variable oxygen-nitrogen gas mixture until the oximeter indicates that arterial saturation has reached the desired level, when the observations are recorded (24). In Figure 2 is illustrated the progressive increases occurring in the mean heart rate, systolic pressure, T wave lowering and RS-T segment deviation of a group of our subjects who were successively studied at 80%, 75% and 70% arterial saturation (25). However, some individuals show marked increases in heart rate at the various levels of arterial unsaturation, while others show almost none (Fig. 3). At the same level of anoxemia, pulse pressure may

*I should like to thank Dr. Bacon Chow for his advice and assistance in regard to electrophoretic analyses.

increase markedly in one individual, remain unchanged in another, and decrease in a third. Measurements on the ballistocardiograph during anoxemia indicate that similar individual differences occur in cardiac output (26). Figure 4 shows some strikingly varied responses at 70% arterial saturation. Subject 51W15 developed a 66% increase in cardiac output, while in Subject 50M30

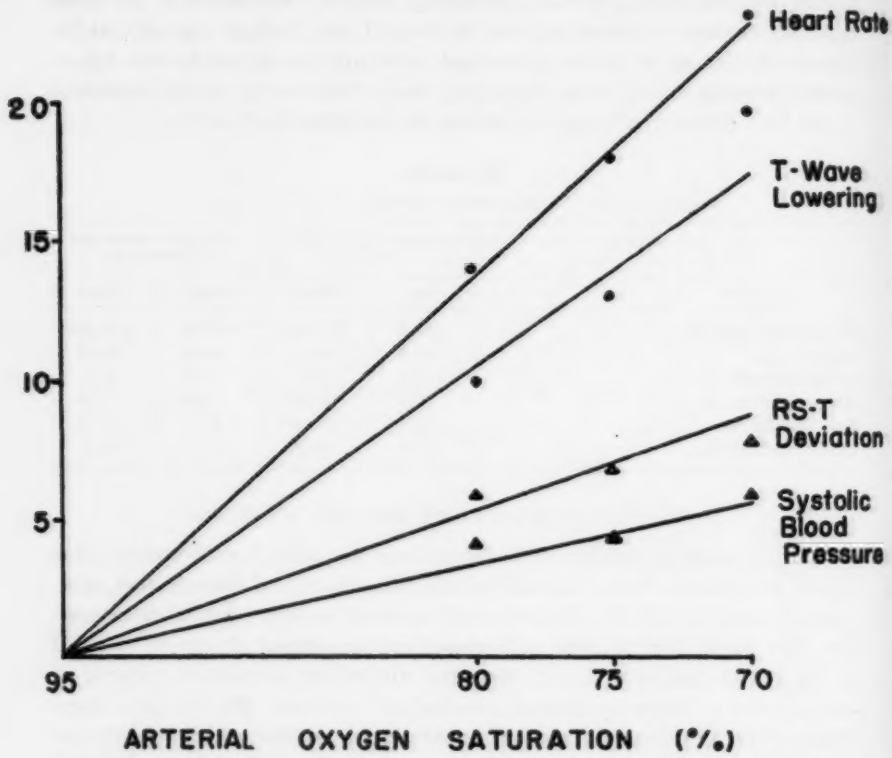


FIG. 2. Changes with progressive lowering of the arterial oxygen saturation. Heart rate change (○) in beats per minute, T-wave lowering (●) in Lead II in tenths of mm., RS-T deviation (△) in Leads I–IV inclusive in tenths of mm., systolic blood pressure (▲) in mm. Hg. Permission from Grune and Stratton.

cardiac output only rose 22%. The close correlation which exists between the change in heart rate and in cardiac output during anoxemia is illustrated here. Whereas Subjects 51W15 and 50M30 show constantly increasing cardiac output as arterial saturation fell, this relationship is not present in Subjects 50M70 and 51M71. Whether or not their failure to increase cardiac output after arterial unsaturation had reached a certain critical level is an important physiologic defect remains to be determined.

Significant differences in circulatory lability are also found after standardized exercise using the double Master test (27). In all instances systolic pressure

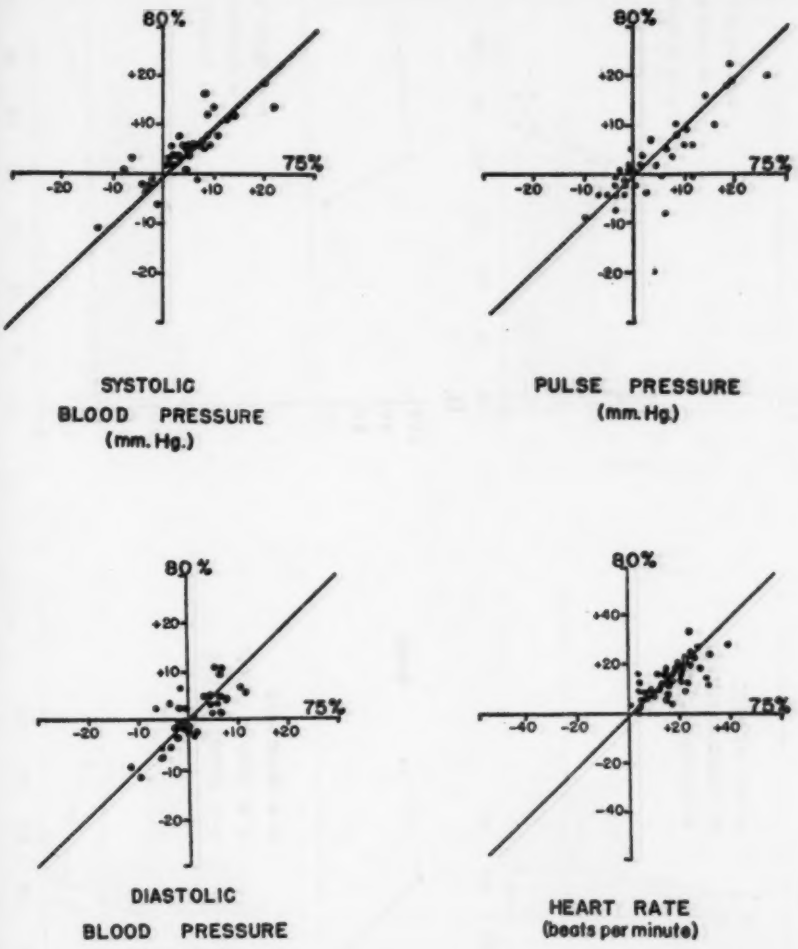


FIG. 3. The response of the same subject to different degrees of anoxemia. Each point represents a comparison of changes noted in one subject at the arterial oxygen saturation indicated along the abscissa and ordinate. Reference lines are drawn at 45 degrees to indicate identical values at the two levels of arterial saturation.

and heart rate increase immediately after exercise; diastolic pressure rises in some subjects, falls in some, and remains the same in others (Fig. 5). The duration of the systolic rise varies considerably from subject to subject (Fig.

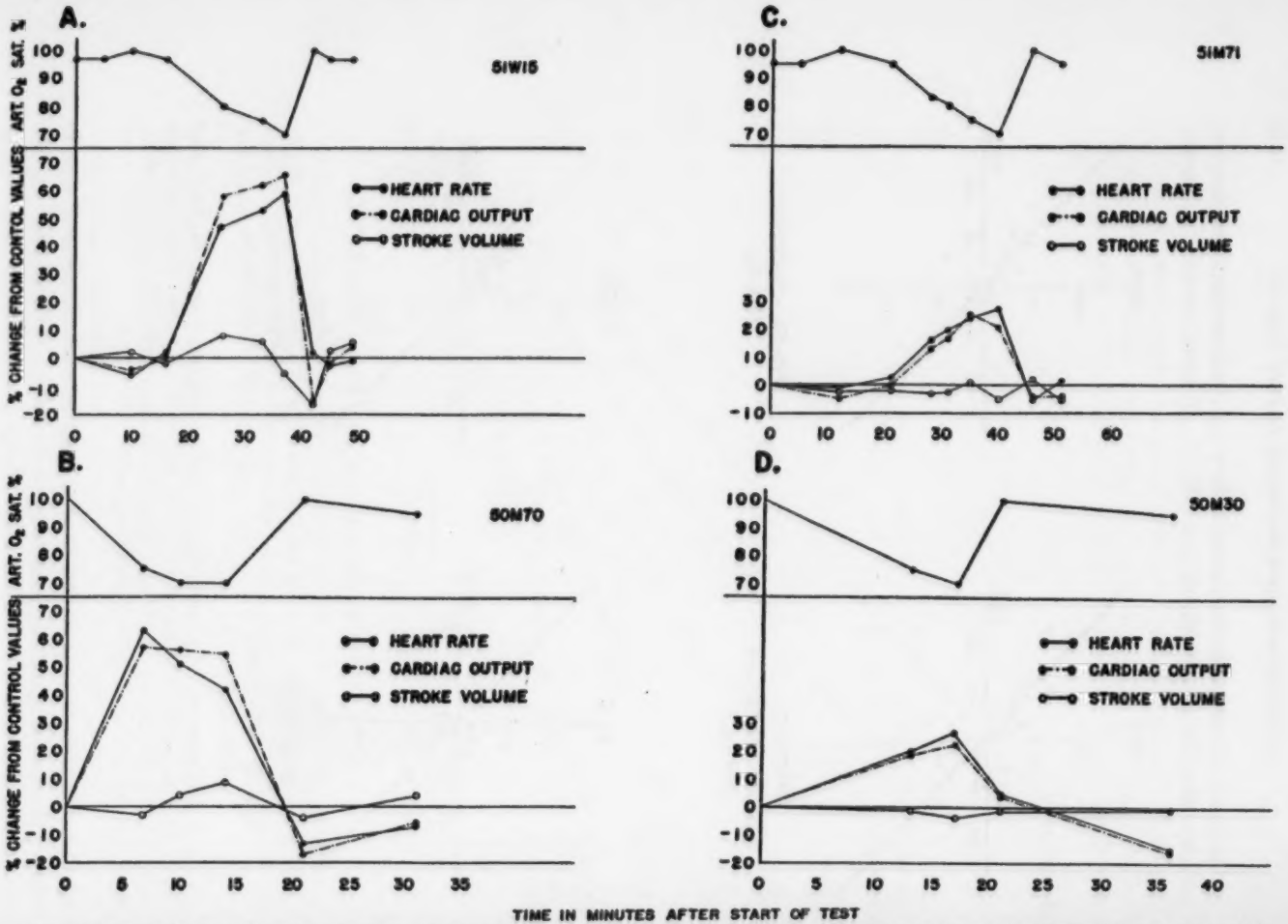


FIG. 4. Different types of cardiac response to anoxemia shown by four healthy subjects as measured by the ballistocardiograph. In each instance arterial oxygen saturation was reduced to 70% in from 15 to 20 minutes. Note the marked increase in cardiac output and heart rate in

6). Those with a delayed return to resting levels lasting from 5 to 12 minutes show no consistent differences from the others in regard to physical training, and none had either myocardial insufficiency or neurocirculatory asthenia,

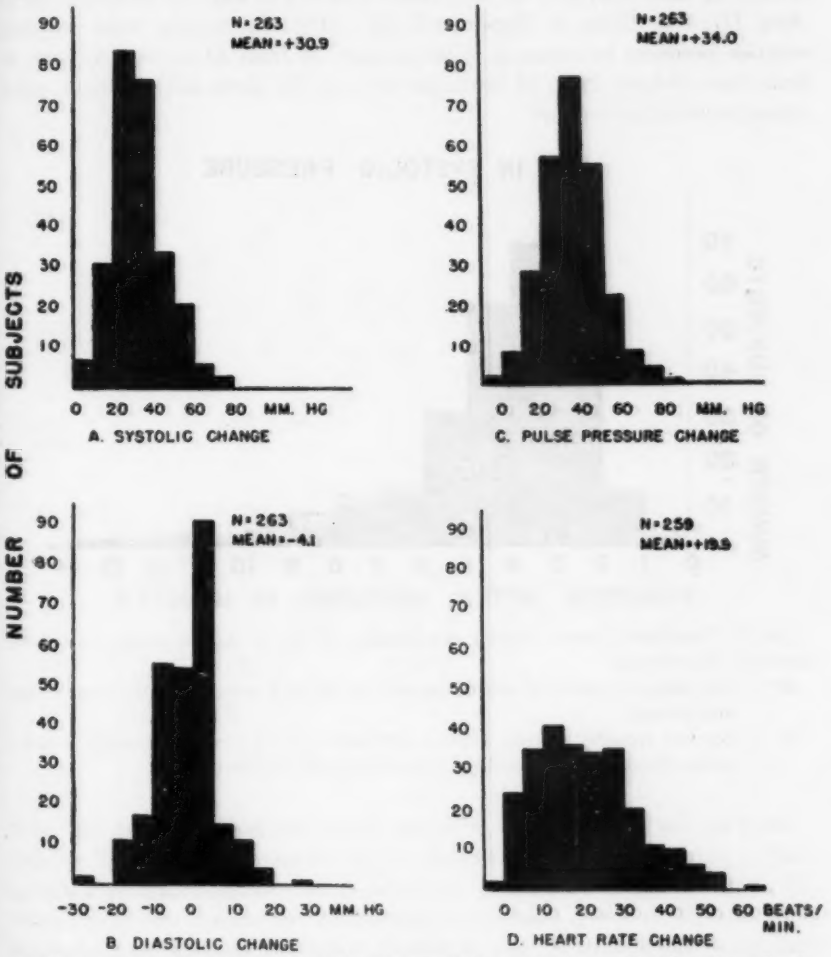


FIG. 5. The distribution curves of the changes after exercise in systolic, diastolic and pulse pressures and in heart rate in all subjects. Blood pressure changes are expressed in mm. of Hg, heart rate changes in beats per minute.

hitherto regarded as the most frequent conditions associated with a prolonged response to a minimal amount of exercise.

A scattergram illustrating the individual types of circulatory response immediately after exercise is shown in Figure 7. Here we see that whereas some

FIG. 4. Different types of cardiac response to anoxemia shown by four healthy subjects as measured by the ballistocardiograph. In each instance arterial oxygen saturation was reduced to 70% in from 15 to 20 minutes. Note the marked increase in cardiac output and heart rate in

TIME IN MINUTES AFTER START OF TEST

subjects show marked increases in *both* heart rate *and* pulse pressure immediately following exercise, others show a marked increase in one but not the other, and some show little change in either. When this scattergram is broken up into quartiles, we find that 15, or 6% of our 259 subjects, fall in Area III, the "Area of Hyperreactivity" (Fig. 8). Among these subjects exercise produces increases in pulse pressure of from 42 to 84 mm., and in heart rate of from 28 to 64 beats per minute. Do these subjects have other characteristics in common?

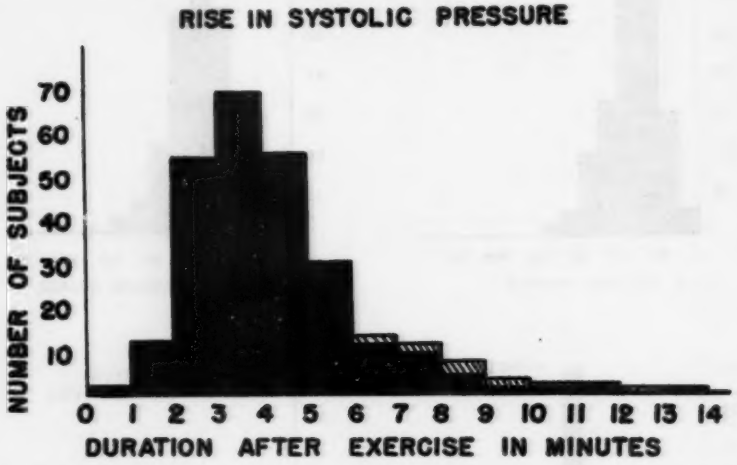


FIG. 6. Distribution curve showing the duration of rise in systolic pressure following exercise in 262 subjects.

▬ = the minute of return of systolic pressure to within 4 mm. Hg of the control level was known.

■ = the last recorded systolic pressure was more than 4 mm. Hg (usually 6 mm.) above the control level, and the total duration was estimated.

They do, for in comparison with our unselected population we find that positive parental history, overweight (20 lbs. or more above "ideal" weight) (28), high resting blood pressure (120 and/or 80 mm. or over), high resting heart rate (80 or over), transitory hypertension (occasional resting or casual readings of 150 and/or 90 mm. or above), transitory tachycardia (occasional resting or casual heart rate of 100 or more), and hyperreactivity to the cold pressor test (a rise of 20 mm. or more in systolic and/or diastolic pressure), are all much more common in the 15 subjects who were hyperreactive to exercise (Table V). The mean resting blood pressure of this group of fifteen is 118.7 mm. systolic and 68.5 mm. diastolic. The individual analyses in regard to these factors are shown in Figure 9. Of the eight students with positive parental

PULSE PRESSURE CHANGE IN MM. HG.

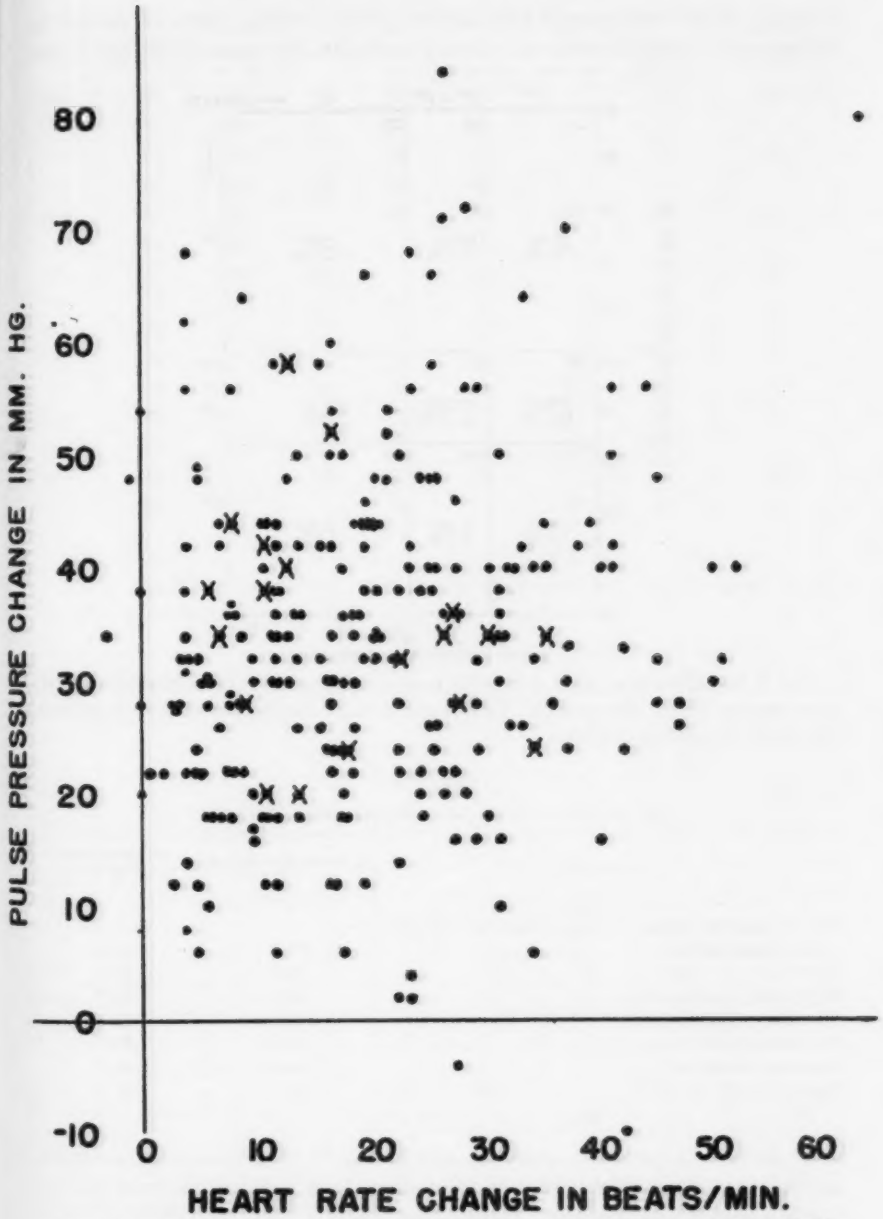


FIG. 7. Relationship of increase in pulse pressure to increase in heart rate immediately after exercise among 259 students. Each point indicates the responses of a single subject. Women are indicated by Xs.

history, all but one parent had suffered from a serious form of disease as indicated by death, a stroke or coronary occlusion. The parental history of two

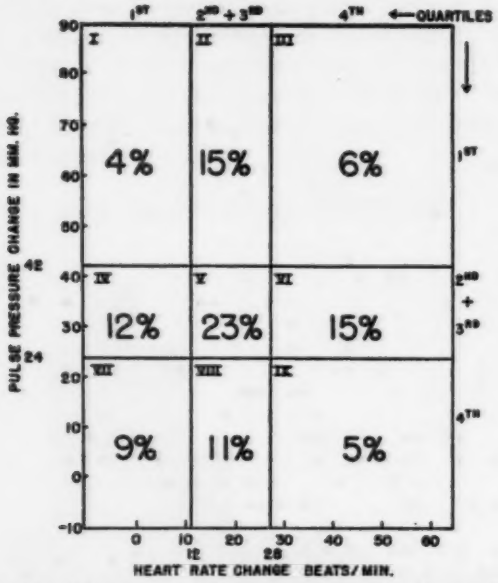


FIG. 8. Relationship of increase in pulse pressure to increase in heart rate immediately after exercise among 259 students. Percentages indicate distribution of total population charted in Figure 7 by quartiles.

TABLE V

*The Significance of Circulatory Hyperreactivity to Exercise*

| INCIDENCE OF: | 15 SUBJECTS IN AREA III % | 257 UNSELECTED SUBJECTS % |
|---|---|---|
| Positive parental history of hypertension and/or coronary artery disease | 53.3 | 23.0 |
| Overweight | 33.3 | 12.1 |
| High resting blood pressure | 60.0 | 26.1 |
| Transitory hypertension | 46.6 | 12.5 |
| High resting heart rate | 33.3 | 10.1 |
| Transitory tachycardia | 20.0 | 11.7 |
| Hyperreactivity to cold | 33.3 | 20.2 |

more subjects is probably positive, and in two it is unknown. In contrast, analysis of a consecutive group of 15 students with negative parental history shows a scarcity of "positive" factors (Fig. 10).

The close correlation between positive parental history and hyperreactivity

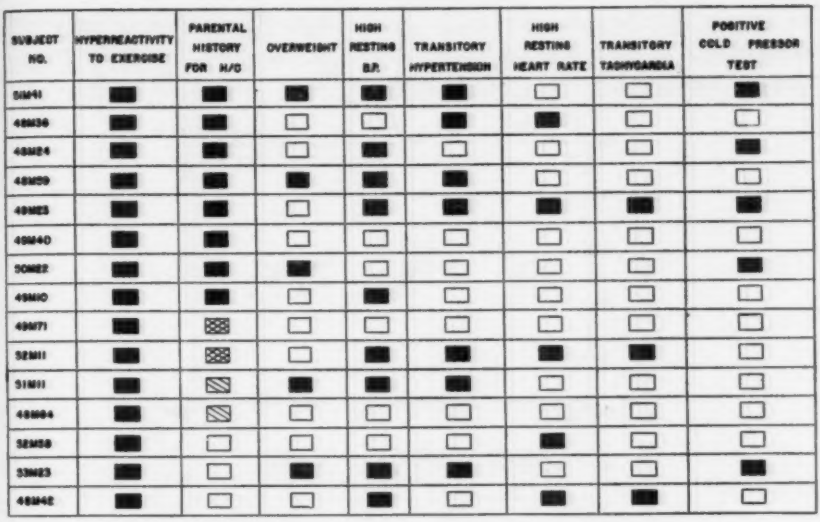


FIG. 9. The individual characteristics of the fifteen subjects with circulatory hyperreactivity to exercise.

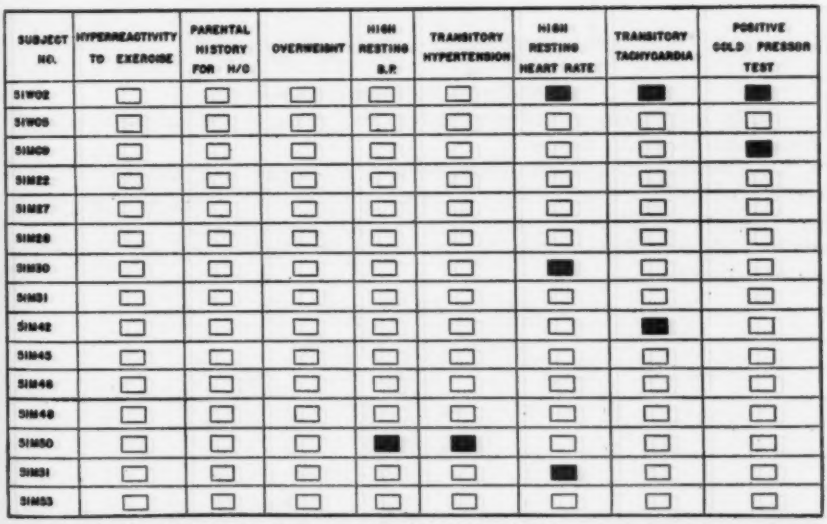


FIG. 10. The individual characteristics of the first fifteen consecutive subjects in one class with negative parental history.

■ = positive.
□ = negative.

to exercise may be demonstrated in another way. Eliminating subjects with questionable or unknown parental histories, the responses of 64 subjects with definite parental hypertension or coronary disease, and of 98 subjects with

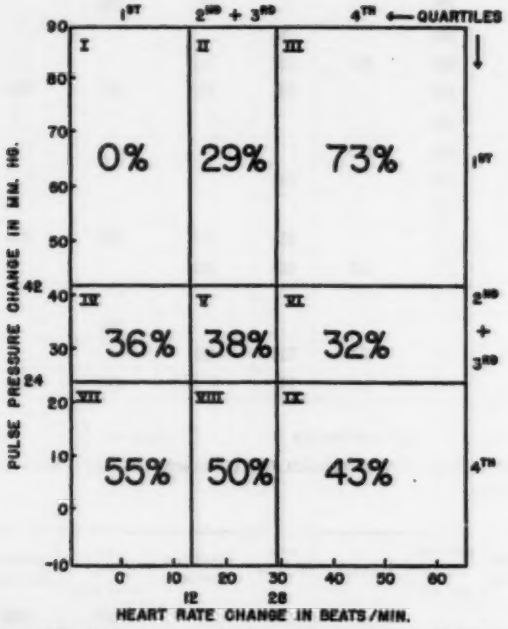


FIG. 11. Relationship of circulatory lability after exercise to parental history of hypertension and/or coronary disease.

A comparison of the immediate response of pulse pressure and heart rate to exercise of 64 subjects with positive parental history for hypertension and/or coronary artery disease and of 98 subjects with parental history negative for hypertension, coronary disease, obesity and diabetes. The percentages indicate the proportion of the subjects in each area with positive parental history.

*Composition of Population Charted*

| PARENTAL HISTORY FOR H AND/OR C | | | | | |
|---|---|---|---|---|---|
| Positive | | Negative | | Total | |
| No. | % | No. | % | No. | % |
| 64 | 39 | 98 | 61 | 162 | 100 |

negative parental history (for these disorders and also for obesity and diabetes) have been charted on the same distribution grid (Fig. 11). Random distribution of these two selected populations would theoretically result in 39% of the subjects in each area having positive parental histories. Actually, 73% of

the subjects falling in Area III, the "Area of Hyperreactivity," have positive parental histories. A different synthetic population in which the 38 subjects with positive parental history for obesity and/or diabetes without known

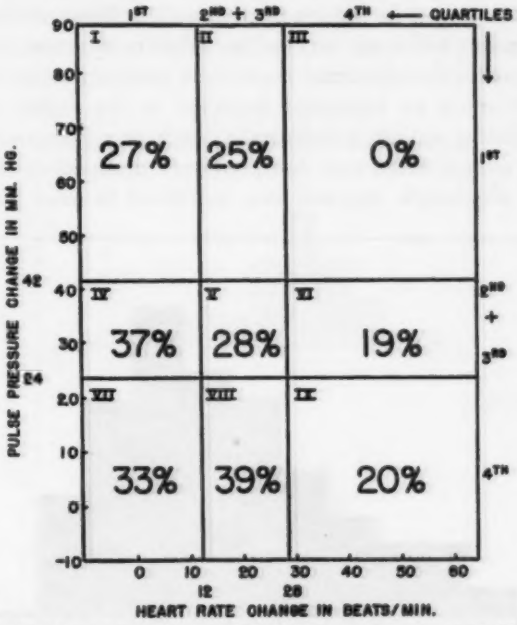


FIG. 12. Relationship of circulatory lability after exercise to parental history of obesity and/or diabetes.

A comparison of the immediate response of pulse pressure and heart rate to exercise of 38 subjects with positive parental history of obesity and/or diabetes and of 98 subjects with parental history negative for hypertension, coronary disease, obesity and diabetes. The percentages indicate the proportion of the subjects in each area with positive parental history.

*Composition of Population Charted*

| PARENTAL HISTORY FOR O AND/OR D | | | | | |
|---|---|---|---|---|---|
| Positive | | Negative | | Total | |
| No. | % | No. | % | No. | % |
| 38 | 28 | 98 | 72 | 136 | 100 |

cardiovascular disease are mixed with the same 98 subjects with negative parental history is charted in Figure 12. *None* of the subjects with diabetic or obese parents fall in the "Area of Hyperreactivity," and they tend to be grouped in the "Areas of Hyporeactivity."

The sodium and water equilibrium of the body is regulated by the adrenal cortex. There is evidence that adrenal cortical activity is of importance in at least certain forms of clinical hypertension. Perera and Blood showed that patients with hypertension fail to lose weight as do normal control subjects following 24 hours of acute sodium restriction (29). They concluded that some disturbance in salt and water metabolism exists in hypertensive vascular disease to account for this abnormal response to sodium restriction.

Their work raises an important question: Is the ability to lose weight promptly following sodium withdrawal a result or a precursor of the hypertension? The sodium withdrawal test provides a means of demonstrating that the *degree* of physiologic response may be related to basic individual differ-

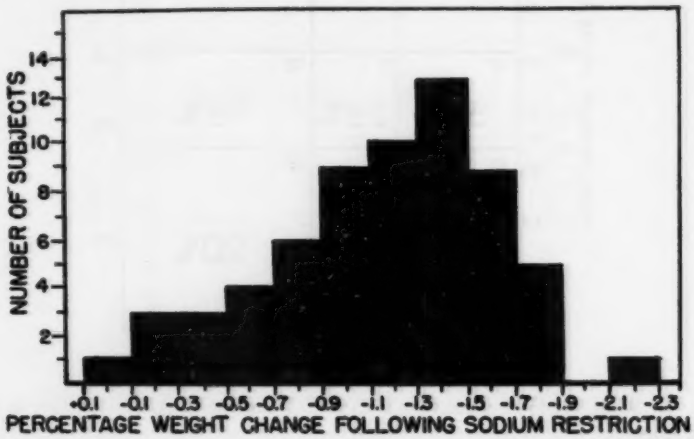


FIG. 13. Distribution curve showing the percentage change in body weight following a 24 hour period of sodium restriction occurring among 64 unselected male students.

ences (30). While the majority of our students undergoing 24 hours of sodium restriction lose corresponding amounts of weight to Perera and Blood's normal subjects, that is, more than 0.9% of body weight, over 20% of our subjects fail to lose that much weight, and thus resemble hypertensive patients (Fig. 13). When our subjects are divided into *two* groups, one consisting of those with parental history of hypertension, or with obesity, high resting blood pressure levels, positive cold pressor test or combinations of these four "positive" factors, and the other group negative in all these respects, it is seen that the weight loss of the "positive" group more closely corresponds with that of the hypertensive patients of Perera and Blood than did the weight loss of the negative group (Fig. 14).

There is no time for detailed description of our studies concerning personality. Previous observers have described personality patterns which charac-

terize patients with hypertension, and also those with coronary artery disease (31–38). These studies, made on patients with established clinical disease, have emphasized the presence of traits such as suppressed hostility, feelings of insecurity, obsessive tendencies and subnormal assertiveness, and have suggested that their existence from early in the life of the individual plays an important and possibly a determining role in the ultimate appearance of hypertension or coronary artery disease. The question therefore arises: Is it

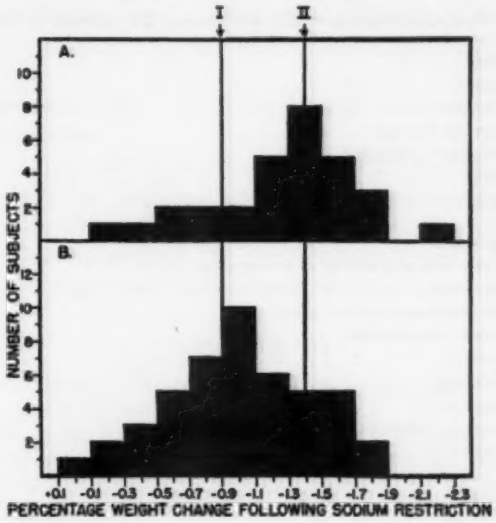


FIG. 14. Distribution curves showing the percentage change in body weight following a 24 hour period of sodium restriction.

A. 30 subjects *without* parental hypertension, overnutrition, high resting blood pressure levels, or vasomotor hyperreactivity.

B. 46 subjects *with* one or more of the above attributes.

I. indicates the borderline between the hypertensive and normal subjects of Perera and Blood.

II. indicates the mean weight loss of our 64 unselected subjects.

possible to identify such distinctive personality patterns in apparently healthy young adults *before* the appearance of one of these diseases?

The difficulties encountered in attempting to measure significant differences in personality are many. We have endeavored to make certain valid observations, however, through the use of a habit survey and the Rorschach test (39). While still incomplete, the results thus far suggest that positive correlations do exist between certain psychologic determinants and our genetic, physiologic and metabolic data. For instance, information has been obtained concerning the types of response of each subject to situations of stress, such

as competitions, examinations and family situations. Each student was asked to choose from a list of 25 types of response all the ones which were characteristic of him. The frequency of the various types of response among 396 medical students is shown in Table VI. At present it appears that subjects with parental history of hypertension or coronary artery disease have differ-

TABLE VI

*25 Habits of Nervous Tension**

396 Medical students gave 2221 responses or 5.6 responses per student

| | |
|---|---|
| A. 6 Usual responses: | |
| 1. General tension | 79% |
| 2. Increased activity | 64% |
| 3. Uneasy or anxious feelings | 43% |
| 4. Increased difficulty in sleeping | 41% |
| 5. Loss of appetite | 38% |
| 6. Urinary frequency | 31% |
| B. 11 Unusual responses: | |
| 7. Urge to confide and seek advice or reassurance | 27% |
| 8. Exhilaration | 22% |
| 9. Tendency to check and recheck work | 22% |
| 10. Anger, expressed or concealed | 21% |
| 11. Philosophic effort | 20% |
| 12. Depressed feelings | 20% |
| 13. Increased urge to eat | 18% |
| 14. Tremulousness or shakiness | 18% |
| 15. Urge to be alone | 18% |
| 16. Diarrhoea | 17% |
| 17. Gripe sessions | 14% |
| C. 8 Rare responses: | |
| 18. Exhaustion or excessive fatigue | 11% |
| 19. Increased urge to sleep | 9% |
| 20. Irritability | 9% |
| 21. Constipation | 5% |
| 22. Decreased activity | 5% |
| 23. Concern about your physical health | 4% |
| 24. Nausea | 4% |
| 25. Vomiting | 1% |

*I should like to thank Dr. Barbara Betz for suggesting many of these habits of nervous tension.

ent patterns of nervous tension from subjects with negative parental history; that subjects with parental history of obesity have certain "unusual" traits in common with subjects whose own blood cholesterol levels are high but whose parents were not obese; and that subjects with low resting blood pressure react to stress quite differently from those with high resting levels.

In closing, I should like to express the hope that studies such as these may serve to awaken new interest in the human settings in which hypertension or

coronary disease begin, and that through closer scrutiny of the interrelationship between many seemingly insignificant differences which exist among healthy young adults, we may at last begin to comprehend how to predict and to prevent the appearance of hypertension and of coronary artery disease.

## SUMMARY

1. A study designed to broaden our understanding of the precursors of essential hypertension and of coronary artery disease is in progress.

2. Using Johns Hopkins medical students as subjects, we are gathering data in regard to individual genetic, physiologic, metabolic, and psychologic patterns.

3. Many previously unstudied interrelationships between these various factors are being analyzed.

4. Preliminary observations at the end of the first four years indicate that positive correlations exist between these different kinds of data, some of which may prove to be significant in the evolution of the diseases in question.

5. Through follow-up studies, the constellations of traits most frequently associated with the early onset of some form of these diseases are to be identified.

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# RHOMBENCEPHALIC CONVULSIVE ACTIVITY*

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The administration of strychnine in doses of from .018 to .022 mg. per kg. intravenously in the cat is followed by the appearance of large rhythmical waves in the electrical tracing taken from the exposed cerebellar surfaces (8). These waves are roughly sinusoidal, with a frequency of 10–30 per second and voltages which are relatively constant for a given preparation but vary from 100 to 400 $\mu$v. in different experiments under similar conditions. Some of the characteristics of this phenomenon have been studied in greater detail and will be discussed here.

## METHODS

In these studies 195 cats, 9 monkeys and 4 dogs were used. Of the 195 experiments on cats, 37 were regarded as unsatisfactory for one reason or another (low blood pressure, excessive hemorrhage, poor general condition, etc.) leaving a total of 158 in this group on which valid observations were made, or a total of 171 experiments.

The animals were anesthetized with ether, 1% procaine injected subcutaneously at the sites of the proposed incisions and the ether discontinued. The trachea was cannulated. Curare or a similarly acting synthetic drug† was injected into the carotid artery in doses sufficient to produce respiratory paralysis, and breathing was maintained artificially.

Silver-tipped bipolar electrodes were placed 2–3 mm. apart in direct contact with the cerebellar and cerebral cortices or with the overlying dura mater. In some cases phonograph needle electrodes were inserted through the intact calvarium so that the tips were in contact with the underlying cortex. When recording from the dentate nucleus, brain stem and spinal cord, electrodes made of enamelled copper wire were used, the positions of which were verified by gross examination or by histological study of the brains.

Tracings were made by a Grass ink-writing eight channel electroencephalograph. In a number of experiments comparative observations were made with a cathode ray oscilloscope and photographs taken of the screen phenomena.

The drugs used in these investigations were administered after a preliminary period of recording. Varying doses were given of strychnine, metrazol, picrotoxin, coramine, caffeine, ephedrine, acetylcholine, eserine, procaine, pentobarbital, nitrogen mustard, tolserol‡ and dichloro-diphenyltrichloro-ethane, penicillin and streptomycin. The drugs were given intravenously, or by injection into the cerebellar cortex and into the region of the dentate nucleus. Some were applied topically to the cerebellum by small pledgets of cottonoid.

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* Aided by a grant from the Lederer Fund of The Johns Hopkins Hospital, Baltimore, Maryland.

† Various preparations were used: intocostrin (E. R. Squibb & Sons, N. Y.), d-tubocurarine (cl. sol., E. R. Squibb & Sons, N. Y.), syncurine (decamethonium Br. C-10), Burroughs, Wellcome & Co., Tuckahoe, N. Y.).

‡ Supplied by E. R. Squibb & Sons, N. Y.

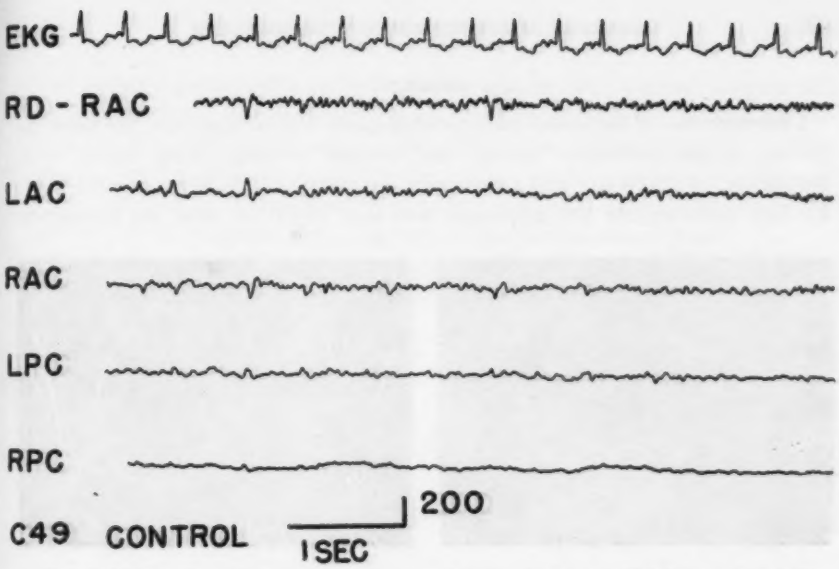


FIG. 1. (C 49) Normal electrocerebellogram of a curarized cat artificially ventilated. Recordings were made with phonograph needle electrodes inserted through the exposed suboccipital bone and in contact with the cortex of the right and left anterior and posterior cerebellar lobes. Trace from the dentate nucleus was made by an enamelled 1 mm. copper wire with exposed tip. In all illustrations the horizontal line at the base indicates a time interval of 1 second and the vertical line a calibration of 200 $\mu$v. unless otherwise stated. Abbreviations used in this and subsequent illustrations are as follows:

BS—brain stem.
DC—distal segment of transected spinal cord.
EKG—electrocardiogram.
LAC, LACB—cortex of left anterior cerebellar lobe.
LD—left dentate nucleus.
LF—left frontal cortex.
LO—left occipital cortex.
LP—left parietal cortex.
LPC, LPCB—cortex of left posterior cerebellar lobe.
LT—left temporal cortex.
L TH—left thalamus.
PC—proximal segment of transected spinal cord.
RAC, RACB—cortex of right anterior cerebellar lobe.
RD—right dentate nucleus.
RF—right frontal cortex.
RG—right gastrocnemius muscle.
RO—right occipital cortex.
RP—right parietal cortex.
RPC, RPCB—cortex of right posterior cerebellar lobe.
RSN—right sciatic nerve.
RT—right temporal cortex.
R TH—right thalamus.
SC—Spinal cord.

## RESULTS

*Characteristics of the control electrocerebellogram.* Recordings from the anterior portion of the cerebellar hemispheres revealed irregular sharp waves with amplitudes of 25–50 μv. and a dominant frequency of 15–18 per second (Fig. 1). Not uncommonly the amplitude was less, 15–30 μv. and the frequency

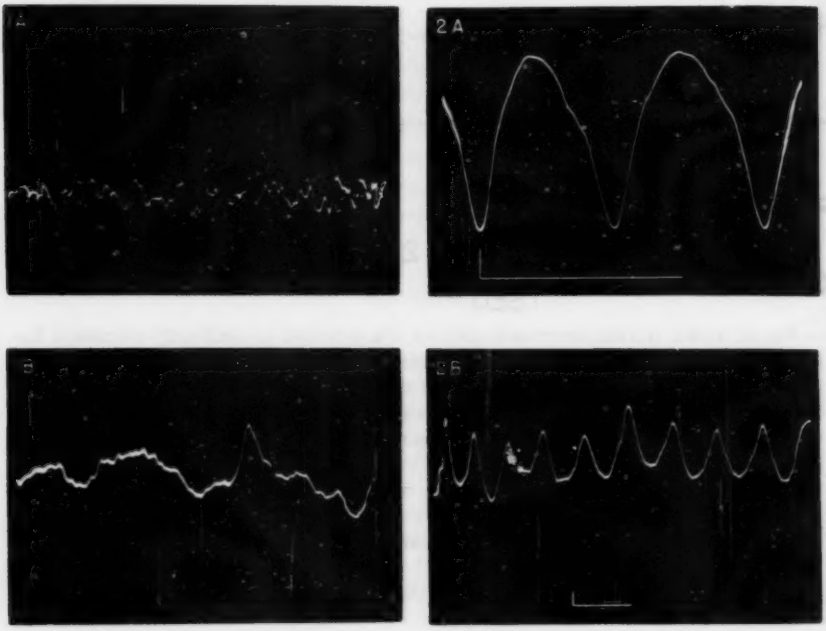


FIG. 2. Oscilloscopic recordings obtained by surface electrodes from the anterior cerebellar cortex of cats prepared under ether and local anesthesia, then curarized and artificially ventilated. Upper records: (C 120) 1A: Control trace from left anterior lobe. 2A: Record 2 hours after injection of 0.4 mg. strychnine into cortex of left anterior cerebellar lobe. Lower records: (C 109) 1B: Control trace from right anterior lobe of another cat. 2B: Record 10 minutes after injection of 0.1 mg. strychnine into the cortex of right anterior cerebellar lobe, showing change in wave form, frequency and amplitude. The horizontal line at the base of the records indicates a time interval of 0.1 second and the vertical line a calibration of 50 μv.

slightly greater. Slow waves of 5–6 per second with voltages of 60–70 μv. occurred irregularly, either singly or in groups. The ascending and descending phases of the sharp waves were of equal rate, but frequently the peaks were somewhat rounded. Voltages recorded from the posterior portions of the cerebellar hemispheres and from the vermis or paramedial lobules were usually less than those from the anterior lobes. These characteristics were not significantly altered whether the recordings were made directly from the exposed cerebellum

with ball-point electrodes or with phonograph needles inserted through the suboccipital bone. The electrographic pattern recorded from the dentate nucleus was not notably different. On the oscilloscope, the electrographic pattern appeared as irregular, very fast activity with a dominant frequency of 150–180 per second (Fig. 2). Throughout there were larger sharp waves with a frequency and amplitude comparable to that seen in the electrocerebellogram.

Although no detailed attempt was made to map out sensory projections to the cerebellum, evoked potentials were frequently recorded as the result of tac-

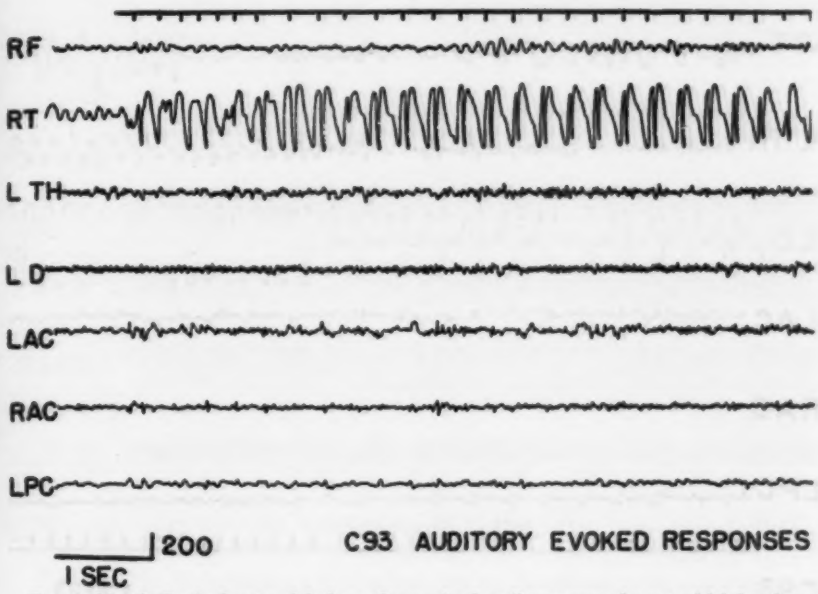


FIG. 3. (C 93) Evoked potentials from the cerebral auditory area of a cat which has been curarized and artificially ventilated. These potentials are of the order of 500 μv. and were elicited by clapping of the hands.

tile, auditory and tendon stimulation. Considerable variation in the amplitude of evoked potentials was noted, depending upon the condition of the animal, the location of electrodes, and the intensity, frequency and duration of stimulus. Auditory evoked potentials appeared as sharp waves of 50–200 μv. recorded simultaneously from the anterior cerebellar lobes while those recorded from the posterior lobes were usually of lower voltage, 35–120 μv., and those from the dentate nucleus 66–132 μv. In one instance auditory potentials from the anterior lobes attained amplitudes of 500–525 μv. (Fig. 3). In the decerebrate preparation, auditory potentials of 30–65 μv. were obtainable from the anterior cerebellar lobes and to a lesser degree from the posterior lobes.

Evoked potentials elicited by tapping the Achilles tendon appeared as sharp waves 60–300 μv., averaging 150–190 μv., in the recording from both cerebellar hemispheres. There was a tendency for the amplitude of the potentials to be greater from the anterior lobe on the stimulated side but this was not always true. Similar potentials were obtained from the dentate nucleus, and in one instance, potentials recorded from this region attained amplitudes of 500–525

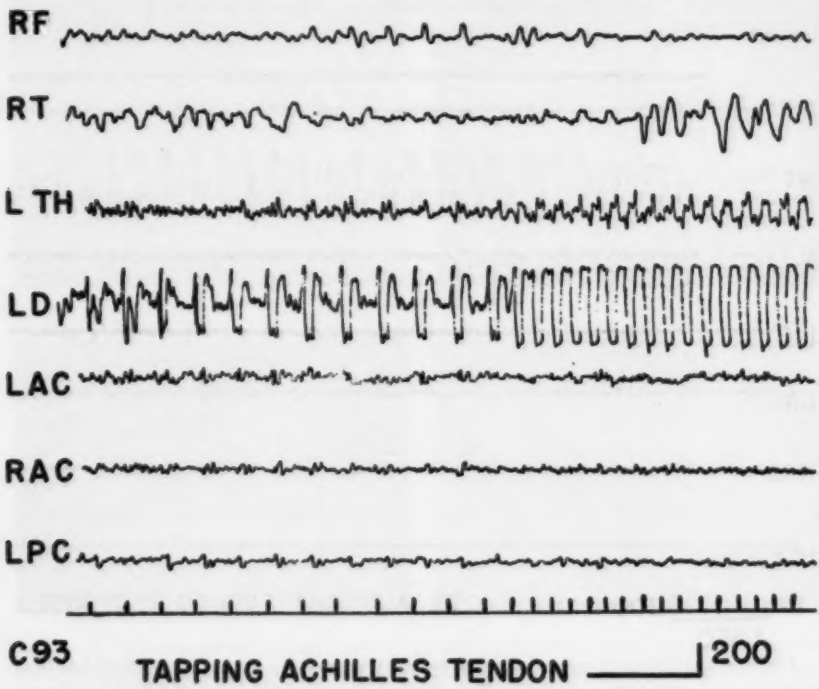


FIG. 4. (C 93) Electrocerebellogram of curarized, artificially ventilated cat. Tapping the left Achilles tendon produces spikes of the order of 500–525 μv. in the trace from the left dentate nucleus. Note the response occurs in the trace from the left thalamus but of lesser amplitude. This effect is also present in the cerebellar traces after a long latent interval.

μv. (Fig. 4). Again, the anterior lobes regularly showed voltages higher than those of the posterior lobes by this type of stimulation.

*Strychnine.* Of the various drugs used in this series of experiments strychnine produced the most notable alterations in the electrocerebellogram. These changes were characterized by the appearance of high amplitude rhythmical waves averaging 100–400 μv. with frequencies of 10–30 per second and continuing for many minutes to several hours. This type of activity could be recorded from all of the accessible cerebellar cortex (parts not accessible were those on the ventral and anterior surfaces—lingula, flocculonodular lobe, paraflocculus).

During such activity in the electrocerebellogram there were no corresponding changes in tracings from representative areas of the cerebral cortex (in the cat, suprasylvian, anterior and posterior ectosylvian and cruciate gyri) (Fig. 5). Occasionally, there was noted a slight decrease in amplitude and a mild increase in frequency of waves from the cerebral cortex during the changes in the electrocerebellogram, but usually there was no apparent alteration in cerebral

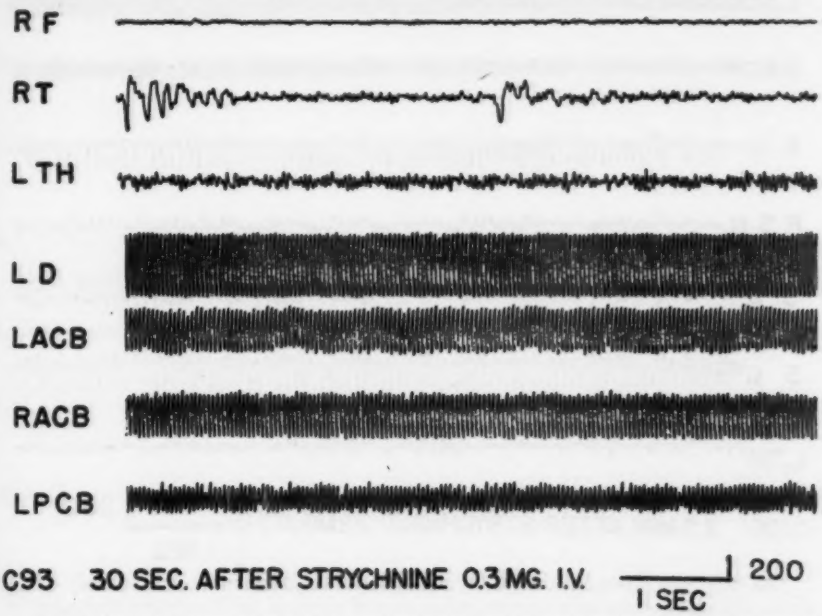


FIG. 5. (C 93) Characteristic high amplitude rhythmical activity in the cerebellogram of the cat 1 minute after the intravenous administration of 0.3 mg. strychnine sulfate. This animal had been prepared in the usual way under ether and local anesthesia, then curarized approximately one hour previously. Frequency of the rhythmical waves is 22–23 per second, while the amplitude in the fourth channel (left dentate nucleus) averages 400–425 μv. Note the uniformity as well as the difference in amplitude between the anterior and posterior cerebellar leads. Also note the relative inactivity of the cerebral cortex.

activity. However, in 15 experiments recordings from the intact spinal cord in cervical, thoracic and lumbar regions at such times revealed high amplitude rhythmical waves of almost identical form and practically synchronous with those in the electrocerebellogram; and in 4 experiments under similar conditions the spinal cord leads showed no activity. In 3 experiments leads were placed upon the sciatic nerve, and in 2 of these instances rhythmical waves similar to those of the cerebellar and spinal cord leads were obtained but of lesser amplitude (Fig. 6).

This type of rhythmical activity could be produced regularly by the admin-

istration of strychnine. Of 83 experiments in which this drug was used in the cat, the characteristic electrical pattern was recorded from the cerebellum in 71 instances (or 85.5%). Of five experiments in which monkeys were used, this activity occurred in 4, while of 4 experiments in which dogs were used, it occurred in one. A typical protocol is given.

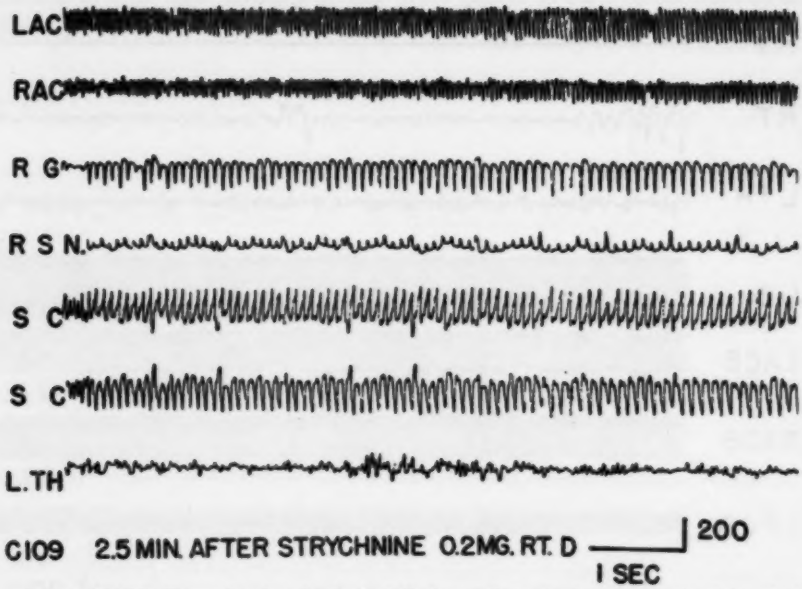


FIG. 6. (C 109) Trace showing rhythmical discharges in leads placed upon the right sciatic nerve, right gastrocnemius muscle and spinal cord of curarized cat 20 minutes after injection of 0.4 mg. strychnine in 4 divided doses into the left dentate nucleus during the preceding 3½ hours. In addition to the usual suboccipital exposure, the midthoracic region of the spinal cord was exposed and bipolar enamelled copper wire electrodes were inserted into the anterior columns. Bipolar silver wire leads were placed upon the exposed sciatic nerve in the thigh and an electromyogram needle was buried in the gastrocnemius muscle under direct observation. The similarity between the muscle and spinal cord activity is interesting.

*Protocol #1* (C 93). November 14, 1949. 2:45 P.M. Cat (2 kg.) Anesthetized with ether, tracheal cannula inserted and 0.3 cc. of intocostrin injected intravenously. Respiration artificially maintained. Ether discontinued.

*3:00 P.M.* Scalp infiltrated with 1% procaine and calvarium exposed. The right cerebellar hemisphere exposed by rongeuring the suboccipital bone; small trephine openings made over the left cerebellar hemisphere and left parietal cortex. Phonograph needle electrodes inserted through the calvarium in the left frontal and temporal regions and into the right and left anterior and the left posterior cerebellar lobes. Insulated copper wire electrodes inserted through the holes in the calvarium into the lateral portion of the left thalamus and left dentate nucleus (verified by autopsy).

*Control record:*—Irregular low voltage fast waves from the right and left anterior cerebellar leads at a frequency of 16 per second and amplitude of 20 to 60 μv.; the same pattern but at a lower amplitude activity from the left posterior lobe. From the left dentate nucleus, the waves were of greater amplitude, i.e., 40 to 70 μv., and averaged 18 to 21 per second. The trace from the left thalamus had a frequency of 17 to 19 per second and amplitude of 50 to 70 μv. with occasional slow waves at 8 per second. The right frontal and temporal records were characterized by spindles every few seconds lasting one to three seconds in which the waves reached maximal amplitudes of 320 to 350 μv. at frequencies of 7 per second (Fig. 7).

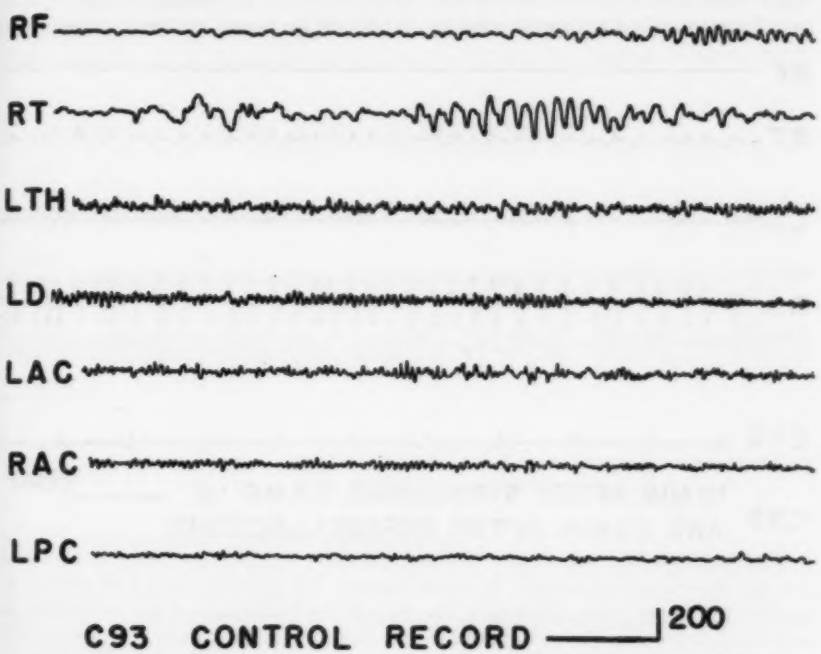


FIG. 7. (C 93) Control electrocerebellogram of curarized artificially ventilated cat described in Protocol # 1. The difference in amplitude between anterior and posterior cerebellar lobes was observed frequently in this series of experiments.

*4:25 P.M.* Clapping hands induced large spikes (450 to 525 μv.) in temporal lead synchronous with each clap and smaller, less evident spikes of 80 μv. in both anterior cerebellar leads (Fig. 3).

*4:35 P.M.* Tapping left Achilles tendon produced large spikes of 475 to 540 μv. in left dentate tracing (Fig. 4).

*5:25 P.M.* Strychnine (0.3 mg.) injected intravenously. Twenty seconds later, the dentate activity increased and almost simultaneously that in the right and left anterior cerebellar channels, while the activity in the left posterior cerebellar was increased a few seconds later (Fig. 5). This developed into a rhythmical pattern of high amplitude waves at a frequency of 22–23 per second. In the left dentate trace the waves average 400 to 425 μv.; in the right

and left anterior cerebellar records 250–275 μv., and in the left posterior cerebellar 160 to 200 μv. During this activity there was no significant alteration in the right frontal and temporal traces, but the left thalamic record had low amplitude activity synchronous with the cerebellar waves.

*5:45 P.M.* The rhythmical activity gradually decreased in frequency to 12–15 per second and became irregular.

*5:50 P.M.* Cerebellum ablated by suction.

*6:10 P.M.* Insulated copper wire electrode inserted into brain stem just to the left of the obex. Trace from brain stem showed large spikes of 400 μv. occurring at regular intervals at a frequency of 4–6 per second unrelated to EKG. Right frontal and left thalamus traces

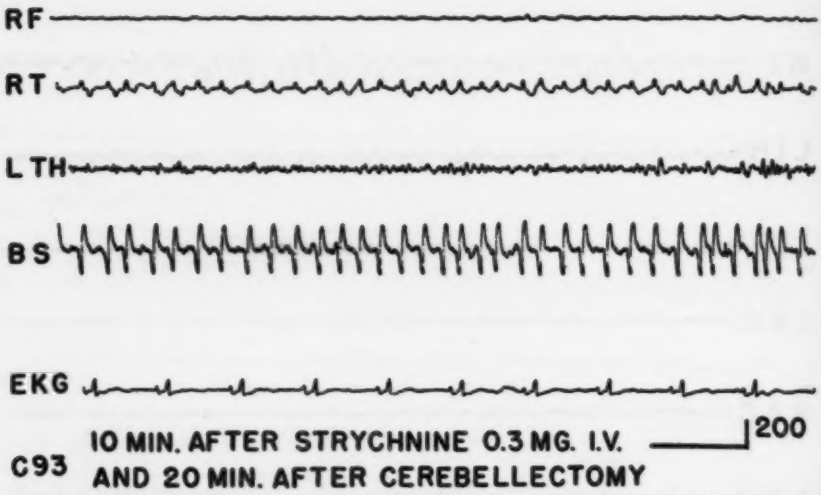


FIG. 8. (C 93) Electrogram of a curarized artificially ventilated cat which had received 0.3 mg. strychnine intravenously 10 minutes earlier. The cerebellum had been ablated by suction 20 minutes before this record. The trace in the fourth channel was made from an enamelled copper wire electrode inserted 3 mm. deep into the brain stem at a distance of 1 cm. anterior to the obex. The rhythmical spikes averaged 400 μv.

remained unchanged, but small waves occurred in the right temporal trace synchronous with the brain stem spikes (Fig. 8).

*6:17 P.M.* Strychnine (1.0 mg.) given intravenously.

*6:18 P.M.* Spikes in brain stem trace suddenly increased in frequency to 11–15 per second and had a rhythmical pattern similar to cerebellar convulsive activity for 10 seconds (Fig. 9).

*6:20–6:36 P.M.* Several additional injections of equal amounts of strychnine were given intravenously with similar responses. Thereafter, the animal's condition rapidly deteriorated and it was sacrificed.

The minimal effective dose, latent period, mode of onset and duration of effect varied according to the route of administration. When given intravenously the minimal dose required to produce the typical strychnine waves in

the cerebellogram of the cat varied between 0.06–0.10 mg. while 0.5 mg. was necessary in the monkey. When the injection was made into the dentate nucleus the minimal effective dose for the cat was 0.1–0.3 mg. and for the monkey 1.0 mg. When the injection was made into the cerebellar cortex, the minimal dose was 0.5–0.6 mg. for the cat. Topical application of 1% strychnine sulfate to the cerebellum of the cat appeared to be ineffectual even after two hours, but with a 2½ % solution of strychnine nitrate applied repeatedly at 2 minute intervals for 2½ hours the characteristic waves appeared at the end of that time in one experiment. The latent period was least following intravenous administration—usually 15–30 seconds—and greatest after topical application of the 2½%

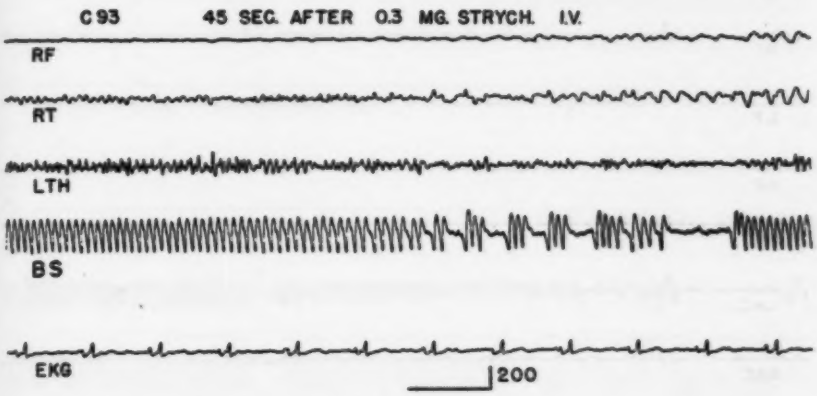


FIG. 9. (C 93) Same preparation as in Fig. 8 but 10 minutes later. An additional injection of 0.3 mg. strychnine was given intravenously 45 seconds earlier (total 0.6 mg.). Compare the fourth channel with that in Fig. 8. Note the frequency has increased markedly but the amplitude remains unchanged.

strychnine solution. When the drug was introduced into the dentate nucleus in doses of 0.3 mg. the high amplitude rhythmical waves appeared in from several minutes to a half hour, while a somewhat longer period elapsed following injection of equal doses into the cerebellar cortex.

The mode of onset of the strychnine waves also varied according to the route of administration. When the drug was given intravenously at or above the threshold doses the rhythmical waves appeared abruptly. This change was apparent in recordings from the dentate nucleus and cerebellar hemispheres simultaneously. The change was usually preceded by a brief discharge of low voltage sharp waves with frequencies of 18–25 per second in all cerebellar channels. These waves rapidly increased in amplitude and became uniform at a

frequency of 28–30 per second and amplitude of 100–400 $\mu$v. Following injections of strychnine into the dentate nucleus and cerebellar cortex, the onset was gradual, with irregular low voltage sharp waves in all cerebellar leads, gradually increasing in amplitude with recurrent fluctuations. After several minutes to half an hour these forms were replaced by the well developed high amplitude rhythmical waves. In three experiments, when strychnine was initially injected into the dentate nucleus of one side, the recording from that region was first to show signs of altered electrical activity (Fig. 10). Less than a second later similar changes appeared in the tracing from the cerebellar cortex of the ipsi-

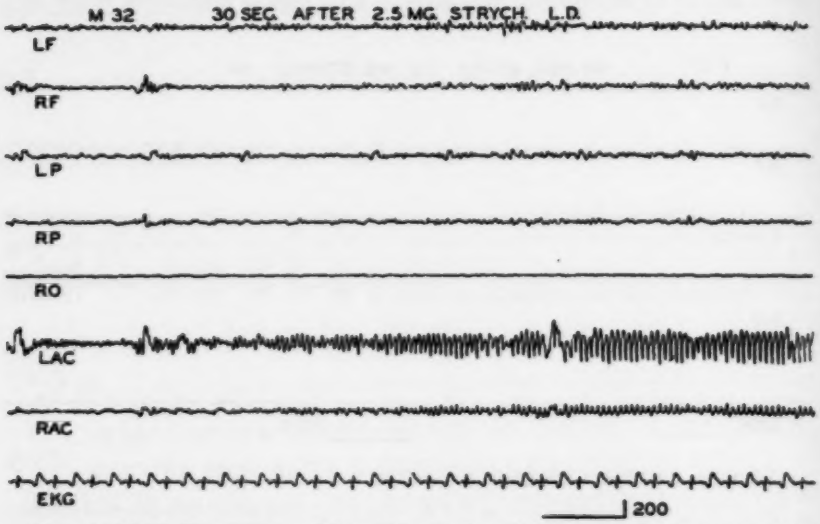


FIG. 10. (M 32) Electrograms of the monkey to show the change in the electrical activity of the cerebellum 30 seconds after the injection of 2.5 mg. strychnine into the left dentate nucleus. The right cerebellar peduncles had been sectioned 22 days previously. Note the onset of cerebellar rhythmical activity on the side of the injection.

lateral anterior lobe and almost at the same time from the opposite anterior lobe.

During well-developed, strychnine-induced discharges, the amplitude and form of individual waves remained quite constant. The typical wave had a sharp peak rising from a concave baseline, with ascending and descending phases of equal rates and duration. The amplitude of successive waves did not vary for long periods in a given preparation. Additional or supraliminal doses of strychnine did not alter the amplitude once the threshold dose had been given. The wave frequency, however, was not always constant during a continuous discharge. Whereas the frequency at the onset was from 26–30 per

second, this rate was not maintained and after a varying period of a few minutes more or less it slowed gradually and was sustained at 18–22 per second. Thereafter, the rate often fluctuated periodically during a given continuous

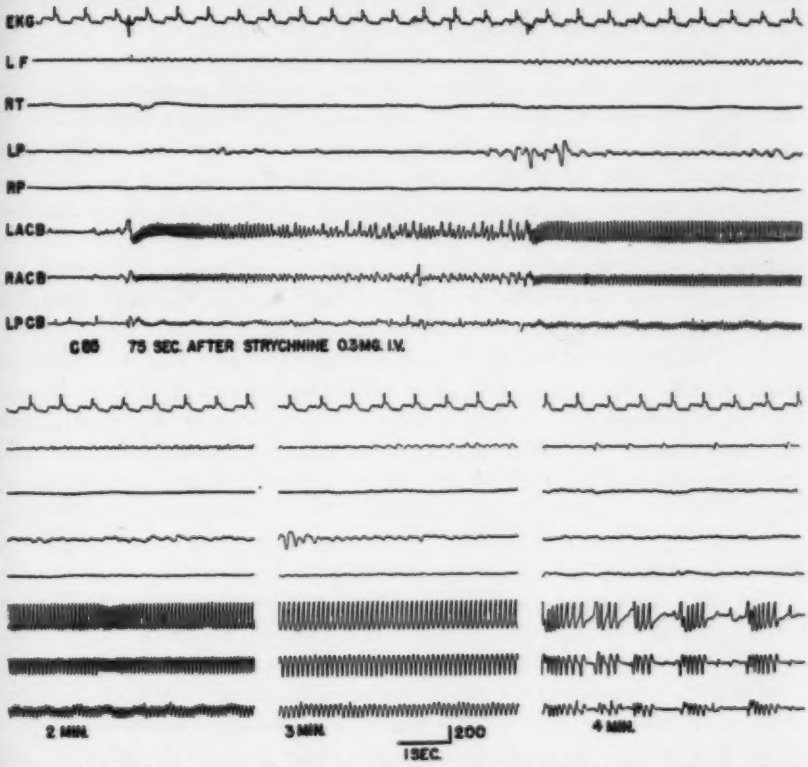


FIG. 11. (C 85) Composite illustration showing various stages during a continuous rhythmical discharge 75 seconds after the intravenous injection of 0.3 mg. strychnine in a curarized cat. The sudden cerebellar seizure activity gradually decreases in frequency, then abruptly changes into sustained high amplitude 400 $\mu$v. waves for 2 minutes. By the end of 3 minutes, the amplitude is unchanged but the frequency has slowed from 15 per second to 10 per second and by the end of 4 minutes has merged into a series of intermittent bursts. The cerebral cortex shows very little activity.

discharge (Fig. 11). Additional doses of strychnine would then cause transient increases in rate. The maximal frequency observed electrographically was 32 per second and the minimal frequency was 8–10 per second. There did not appear to be a direct correlation between frequency and amplitude. In many experiments voltages of 400 $\mu$v. at 26–30 per second were seen, while just as often waves of 100 $\mu$v. at the same rate were seen. Again, with amplitudes of

400 μv. the frequency was not unusually as slow as 10 per second (C 49), while the same rate was often seen in waves of only 100 μv. The form and frequency of waves did not vary according to the region under recording, but a regular difference in amplitude between waves recorded from the anterior and posterior cerebellar lobes was noted, waves from the latter usually being about 50% less in height.

Oscilloscopic recordings of the cerebellum during high amplitude rhythmical discharges revealed wave forms, frequencies and amplitudes practically identical with those observed in the ink-tracings from the same areas. The waves were smooth, with broad bases, sharp peaks and did not show superimposed high frequency ripples. In the recordings made from the cerebellar hemisphere of monkeys and dogs the rhythmical waves were less well developed. The main difference in this respect was that in the monkey and the dog the amplitude was notably less than in the cat and more variable, but the wave form, frequency and general pattern were practically identical.

The duration of strychnine-induced rhythmical waves was dependent, in part, upon the route of administration. When the drug was given intravenously at threshold doses, the rhythmical waves continued for 10–30 minutes; and, when given into cerebellar cortex, they lasted 1–2½ hours. Usually the individual discharge had a duration of 30 seconds to 3 minutes, recurring thereafter at intervals of 1–3 minutes for 30–60 minutes. The longest continuous discharge was 30 minutes in one experiment, while the longest period of intermittent rhythmical activity without additional doses was 4 hours.

Individual discharges of greatest amplitude and frequency were obtained by intravenous injections, while frequencies as low as 10 per second were seen only after the discharges had been in progress for long periods—i.e., 15–30 minutes —or at the termination of the rhythmical activity. Continuous rhythmical discharges after variable periods were replaced by intermittent spontaneous bursts of identical pattern but of short duration—usually 1–3 seconds. At such times it was possible to precipitate continuous discharges by afferent stimuli. Clapping one's hands would initiate this activity as would a metallic clicker. Tapping the Achilles tendon would likewise produce a rhythmical discharge after several rapid taps (Fig. 12).

In 17 experiments where the brainstem was sectioned at the intercollicular level during spontaneous rhythmical discharges, the characteristic pattern could still be recorded from the cerebellum in 10 of these after a recovery period of from 5–30 minutes. The electrocerebellogram in these cases showed no significant changes, while the tracings from cerebral leads were flat. In those 7 experiments where the rhythmical waves did not reappear in the cerebellogram after brainstem section the animals appeared to have died of shock and autopsies showed extensive hemorrhages at the base of the brain and in the thalamus and hypothalamus. Conversely the characteristic strychnine-induced rhyth-

mical waves could be recorded from the cerebellum in preparations in which brainstem section had been performed prior to administration of strychnine, and this was observed in 4 instances (Fig. 13).

In 5 experiments ether was introduced into the respirator tube of the curarized animal in which strychnine-induced rhythmical waves were being recorded. Within a few seconds the electrical pattern was changed to irregular low-voltage sharp waves. After one minute, there was rapid depression of all electrical activity, but if the ether were discontinued, the rhythmical activity gradually reappeared within 2 to 3 minutes (Fig. 14). Under similar conditions,

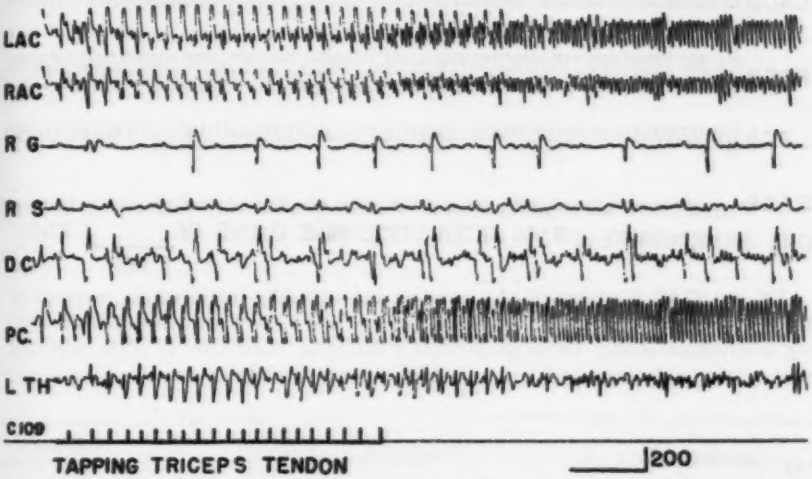


FIG. 12. (C 109) Electrocerebellograms of a curarized and artificially ventilated cat which had received 0.4 mg. strychnine into the dentate nucleus in 3 divided doses within 3 hours. The spinal cord was divided one hour before this tracing. Tapping the triceps tendon initiated a rhythmical discharge. Seizures initiated in this fashion continued for 1–3 minutes and could be elicited at will by repeating the stimulus.

in 10 instances, simply clamping the respirator tube for 2 minutes was followed within 15–20 seconds by rhythmical waves of increased frequency (but with amplitude unchanged). This effect persisted for 30–60 seconds, at which time the waves ended abruptly. Within one minute after releasing the clamp, however, the rhythmical waves reappeared (Fig. 15).

*Caffeine, coramine and ephedrine.* The injection of 0.03 cc caffeine sodium benzoate (.015 gm.) into the cerebellar cortex caused no significant alteration in the cerebellogram in 3 instances. Intravenous administration on 5 occasions of as much as 0.5 cc of caffeine did not produce any notable changes. Coramine (25% solution) applied topically to the cerebellar cortex of 6 cats and 2 monkeys failed to produce any changes in the cerebellar tracings, and when given

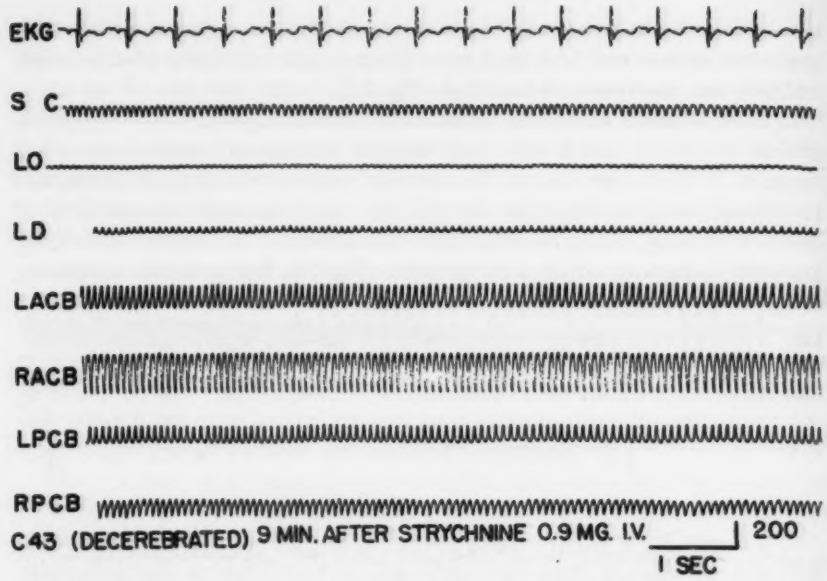


FIG. 13. (C 43) Electrograms of a curarized and artificially ventilated cat, prepared by Bremer's encéphale isolé technique, 17 minutes after the intravenous administration of 0.9 mg. of strychnine sulfate. The occipital cortex is isoelectric. The uniformity of the individual waves of the cerebellum is striking and lasted for almost 5 minutes.

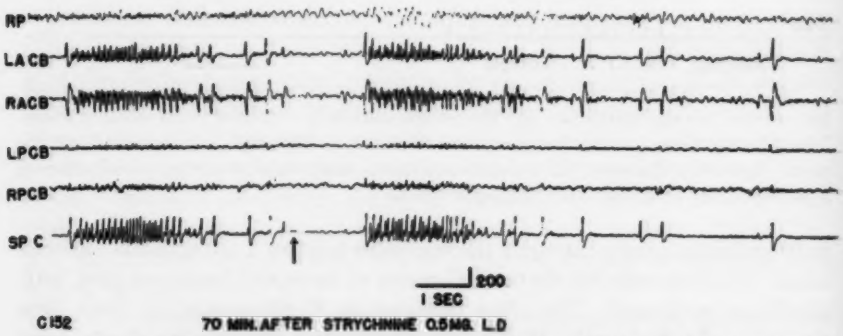


FIG. 14. (C 152) Electrocerebellogram of a curarized artificially ventilated cat taken 70 minutes after 0.5 mg. strychnine had been injected into the left dentate nucleus, showing the effect of ether inhalation upon strychnine activity. Arrow denotes point where ether was introduced into respirator tube. Within 10 seconds the rhythmical waves ceased and did not reappear until 5 minutes after ether was discontinued.

intravenously in doses of from 0.13–0.75 gm. or when injected into the cerebellum itself in doses of 0.03–0.75 gm. was likewise without effect. Ephedrine similarly administered was not observed to produce significant changes.

*Picrotoxin and metrazol.* Single or repeated injections of 0.3% picrotoxin in doses of 0.03 cc (0.00009 gm.) were given into the cerebellar cortex or dentate nucleus in 5 cats and one monkey and doses of 0.003 gm. metrazol were given by the same route in 6 cats and 5 monkeys. In none of these cases did rhythmical waves appear. Doses of 0.0015–0.009 gm. of picrotoxin or 0.05–0.3 gm. of

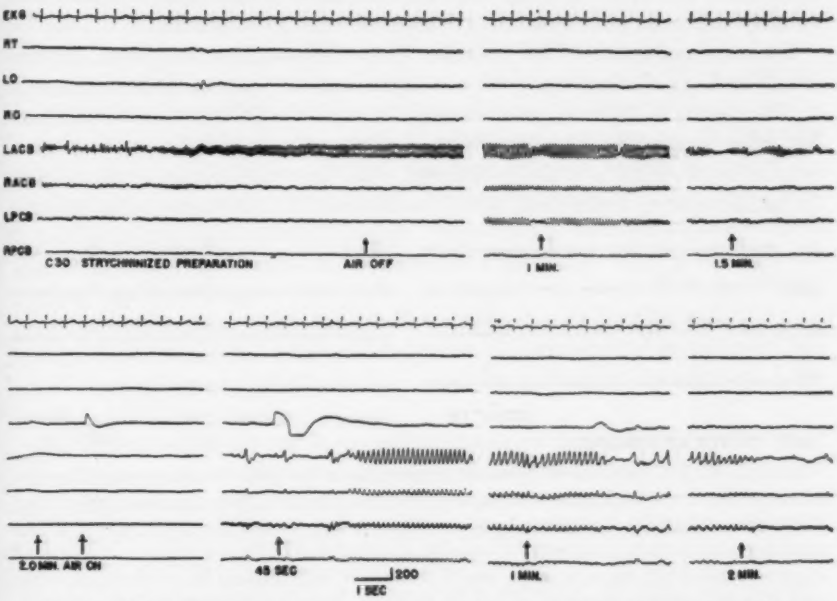


FIG. 15. (C 30) Electrocerebellogram of cat showing effect of anoxia upon strychnine activity. Curare was given 5 hours previously and 0.5 mg. strychnine was injected into the cerebellar cortex in 3 divided doses within 3 hours. First arrow denotes beginning of anoxia. After one minute of anoxia the amplitude in channel 4 remained at 240–280 $\mu$v. while the frequency had decreased from 10 per second to 12 per second; but in the last 3 cerebellar channels the amplitude showed a marked increase. By the end of 1.5 minutes of anoxia the activity had nearly ceased, and by the end of 2 minutes' anoxia electrical activity was absent in all leads. Upon restoring artificial respiration the rhythmical waves reappeared after 45 seconds.

metrazol given intravenously in 5 cats were followed by seizure patterns in the cerebral and cerebellar leads but without evidence of prolonged independent rhythmical waves in the cerebellogram. Repeated topical applications of 10% metrazol or 0.3% picrotoxin to the cerebellar folia in many instances were without apparent effect.

*Acetylcholine and eserine.* Acetylcholine was injected into the cat's cerebellum in doses ranging from 0.0075–6.0 mg. in 5 experiments or given intravenously in corresponding doses in 4 experiments. The latent interval, duration of effects

and degree of change were directly proportional to the amount given. Doses of 1.0 mg. or over were followed by depression of electrical activity. Eserine ¼% was given independently of ACh in doses of 0.0075–6.0 mg. into the cerebellar cortex in 8 experiments and intravenously in 5 experiments without producing changes in the electrical activity. However, when eserine ¼% was applied to the cerebellum within 2–5 minutes after ACh the depressive response to ACh was notably enhanced but rhythmical discharges were not observed.

*Procaine and pentobarbital.* Procaine (in a 1% solution) was given intravenously in 8 experiments upon the cat. Injections of 1% procaine intravenously in 10 cc amounts (10 mg.) had no significant effect on the cat's cerebellogram but when larger amounts were given—i.e., over 15 cc (150 mg.)—progressive depression of electrical activity occurred until the record became entirely flat. In one interesting experiment (C 151) a total of 32 cc procaine hydrochloride

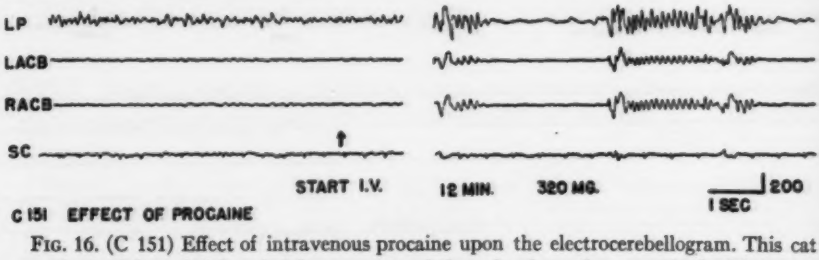


FIG. 16. (C 151) Effect of intravenous procaine upon the electrocerebellogram. This cat was etherized for a brief period for exposure of the calvarium, then curarized with 0.4 cc. intocostrin and artificially aerated. In this experiment the only drug administered was a slow continuous intravenous injection of 1% procaine hydrochloride. Twelve minutes was required to give a total of 320 mg. of procaine and at that point these unusual waves appeared in the cerebellar and cerebral tracings.

(320 mg.), given intravenously at the rate of 0.5 mg. per second, had a singular effect on the cerebellogram. After 150 mg. were given the dominant frequency disappeared gradually and was replaced by brief bursts of large waves (150–200 μv.) at a rate of 8–12 per second (Fig. 16). The bursts had durations of from 2–4 seconds and recurred every 3–10 seconds. Between bursts the record was isoelectric. This type of activity appeared in the cerebellar leads and cerebral traces synchronously. An additional 150 mg. did not alter the pattern and the activity continued for about one hour.

One per cent procaine hydrochloride (0.03–0.3 cc) injected into the cerebellum in 4 cats was without effect. Similar injections into the dentate nucleus and cerebellar cortex in several cats during strychnine-induced rhythmical activity did not abolish the fit.

Sodium pentobarbital (65 mg. per cc) administered intravenously was followed within 10–15 seconds by interruption of strychnine-induced rhythmical waves in the cerebellar electrogram and depression of electrical activity.

*Antibiotic agents.* Many of the antibiotic substances have been shown to have convulsive properties when applied to the cerebral cortex (14). Penicillin in doses over 5,000 units injected into the cerebellum of the intact but curarized cat in 7 experiments has given rise to fast spiky activity from the occipital cortex, the spikes appearing almost simultaneously on the two sides. Usually lower amplitude spikes are present in the cerebellum on the side injected but not on the other side. From 10–60 minutes after the injection, a generalized epileptic cortical activity usually occurred with marked spiking of the cerebellum on the side injected and small spikes on the opposite side. The amplitude and form of the occipital lobe spikes appeared to be the same on the two sides.

In the "encéphale isolé" preparation, penicillin in amounts of 10,000 units or more injected into the cerebellum has been followed within 5 minutes by slow twisting movements of the head and wild movements of the limbs, particularly the contralateral hind limbs in 3 experiments. Electroencephalographic studies of such preparations immobilized by curare in 10 experiments did not produce significant alterations in the electrocerebellogram. In 3 decorticate preparations similarly treated the findings were equally insignificant.

Streptomycin injected into the cerebellum (3 experiments) or topically applied (2 experiments) failed to induce cerebellar spiking in the absence of the cerebral hemispheres.

*Nitrogen mustard.* Of the many drugs employed in these studies, the only ones other than strychnine capable of producing prolonged rhythmical high amplitude waves in the electrocerebellogram were nitrogen mustard and dichloro-diphenyltrichloro-ethane. Local injections of nitrogen mustard into the cerebellum in doses of from 1.0–18.0 mg. was carried out in 6 experiments without apparent effect. In one interesting experiment the intravenous injection of the drug produced rhythmic fast waves in the electrocerebellogram (Fig. 17) which were practically identical with those induced by strychnine. The protocol of this experiment is given.

*Protocol #2* (C 135) 11:09 A.M. March 17, 1950. Preparation as in protocol #1. Phonograph needle electrodes were introduced through the calvarium in the right and left frontal, parietal, occipital and sub-occipital regions. After making a mid-thoracic laminectomy, one pair of electrodes was placed in anterior columns of spinal cord. The control record from the suprasylvian cortex showed irregular low voltage sharp waves of 20–60 μv. at frequencies ranging from 10 to 14 per second and occasional bursts of high amplitude sharp waves of 220–280 μv. at 6 per second lasting 0.5–1.0 seconds. Tracings from the surface of right and left anterior cerebellar lobes were of uniform low voltage slow waves of 20 μv. or less of 12–14 per second. The left posterior cerebellar lobe tracing was quite similar although the amplitude averaged 20 μv. greater, while the tracings from the right posterior cerebellar lobe and from the thoracic cord were isoelectric.

*1:04 P.M.* Nitrogen mustard started intravenously by a slow continuous injection.

*1:05 P.M.* Total of 7 mg. nitrogen mustard given. At this point low voltage fast waves appeared from right anterior cerebellar lobe and spinal cord. When 9 mg. nitrogen mustard

had been given these waves increased to 22 per second at 20–40 μv. and were more pronounced in the cord leads.

*1:06 P.M.* Ten seconds after the total dose of 10 mg. had been given, there was a marked increase in activity in the cord leads, the waves increasing to 200–360 μv. at 25 per second (Fig. 17). At the same time there was a corresponding change in all other cerebellar leads but of lesser amplitude. The left and right anterior lobes showed low voltage fast waves at 20–60 μv. and 21 per second, the posterior lobes showed fast waves at 22 per second and 20–100 μv. In the cerebral cortex there were no marked changes except in the left suprasylvian region where appeared large irregular slow waves of 200 μv. at 4–5 per second with superimposed waves of 20–40 μv.

*1:06–1:25 P.M.* Rhythmical activity recurred intermittently. Passive stretching of gastrocnemius produced diminution of rhythmical waves, or at times, abolition of same. Auditory stimuli produced bursts of rhythmical waves. Irrigation of right ear with ice water appeared to have no effect on the rhythmical waves. Animal succumbed after cutting spinal cord.

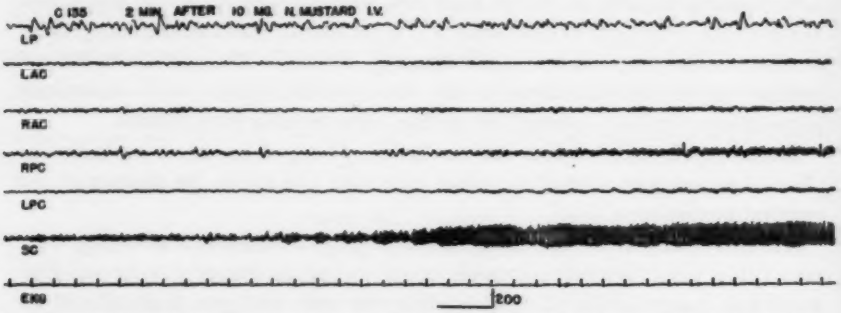


FIG. 17. (C 135) Electrocerebellogram of curarized and artificially ventilated cat showing the brainstem-cerebellar activity 2 minutes after the intravenous injection of 10 mg. nitrogen mustard.

In 7 other experiments in which nitrogen mustard was given intravenously, no such activity developed, even with as large a dose as 20 mg. Instead, in these cases, there was progressive depression of all electrical activity with its complete disappearance and non-recovery.

*Tolserol.* In 5 experiments in which the animals had been strychninized and rhythmical discharges were occurring in the cerebellogram, it was possible to diminish or abolish the rhythmical waves with tolserol (Fig. 18). When the drug was given intravenously at the rate of 0.5 mg. per second, depression of voltages became evident when 20.0 mg. had been given. Within 3 minutes thereafter, the tracings from the cerebellum and spinal cord became flat, while the cerebral activity showed no significant alterations. However, this effect of tolserol was but temporary and within 9–10 minutes the cerebellogram returned to its previous condition and rhythmical waves reappeared. As little as 10.0 mg. of tolserol intravenously produced definite depression in the curarized, unstrychninized cat in one case, while as much as 140 mg. was lethal.

*Dichloro-diphenyltrichloro-ethane* (*DDT*). Five cats were fed a diet containing 300 mg. of crystalline dichloro-diphenyltrichloro-ethane daily for periods ranging from 4 days to 2 weeks. Two died before electrographic studies were made. Each of the remaining animals showed signs of toxicity within one or two days

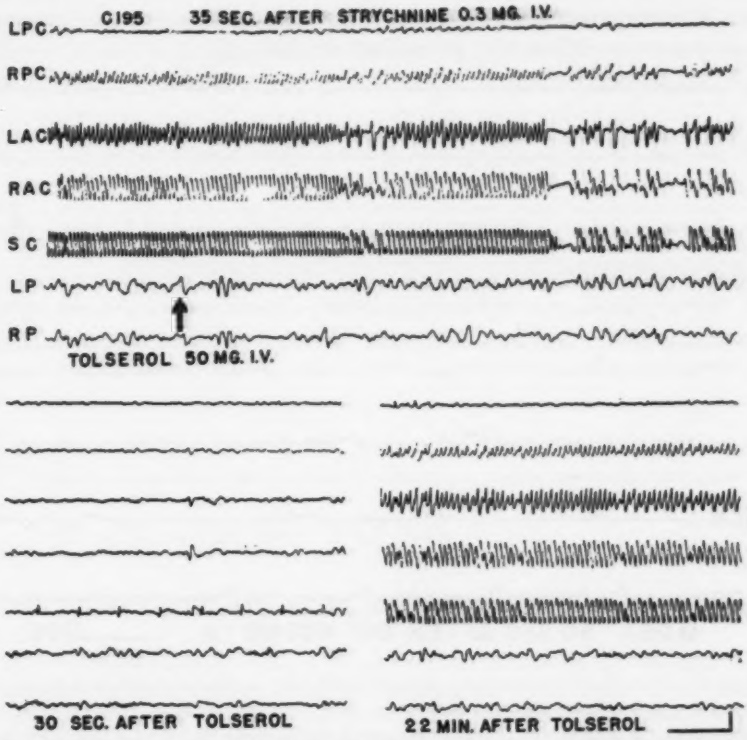


FIG. 18. (C 195) Electrocerebellogram of a curarized cat, showing the effect of 50 mg. tolserol upon strychnine convulsive activity. The first trace was made 35 seconds after the intravenous injection of 0.3 mg. strychnine and shows the end of the tolserol injection. The second trace was made 30 seconds later. Note that the cerebral cortical activity is practically unchanged while the rhythmical waves have disappeared. The third trace was made 22 minutes after tolserol was given. The strychnine convulsive activity is like that in the first trace.

before the total dose of 3200 mg. was reached. There were generalized irregular tremors, ataxia and weakness. The animals were then prepared in the usual manner.

The control electrocerebellogram was characterized by a marked irregularity. The amplitude was from 35–75 $\mu$v. with a dominant frequency of 25–27 per

second. There were many spiky waves of 100–165 μv. and numerous irregular slow waves of 5–8 per second at 50–75 μv.

The usual doses of strychnine capable of inducing prolonged rhythmical discharges in the electrocerebellogram were not followed by this type of activity in cats fed on a dichloro-diphenyltrichloro-ethane diet. When strychnine was given in such preparations, the only change was a mild increase in frequency. Large doses were followed by generalized cerebral spiking.

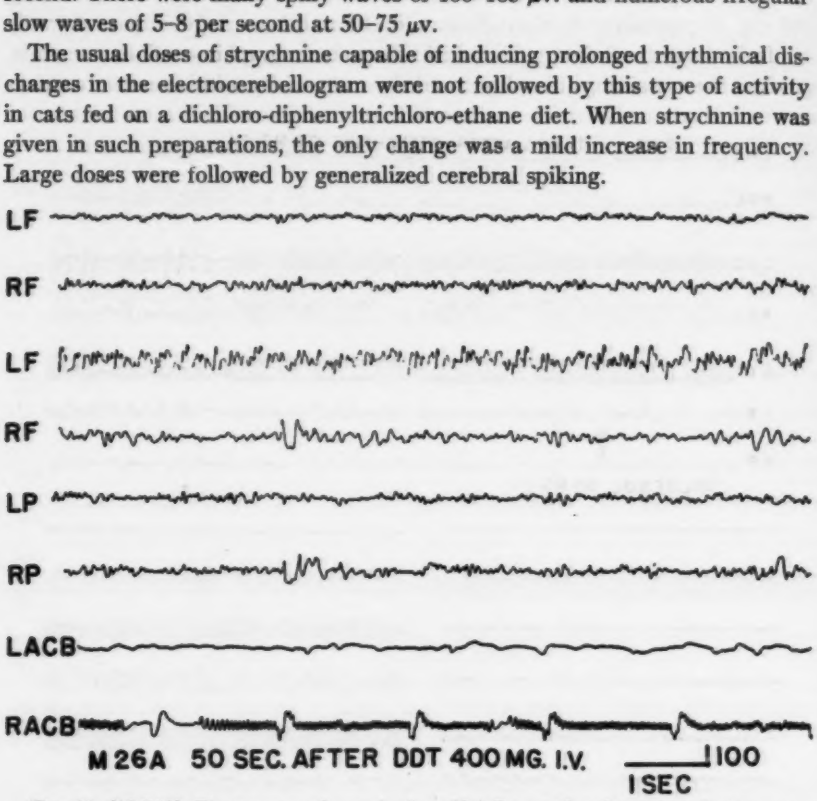


FIG. 19. (M 26A) Electrogram of curarized, artificially ventilated monkey during a continuous slow intravenous injection of 400 mg. (5% solution) of DDT. The injection was stopped with the appearance of rapid rhythmical waves of 40–50 μv. at a frequency of 30 per second in the cerebellar channel. The form and frequency of the waves resemble those seen in the strychnine seizures. In these traces, the vertical line on the scale represents a calibration of 100 μv.

A 1% solution of dichloro-diphenyltrichloro-ethane injected intravenously (.2–.3 gm.) or locally into the cerebellum of 3 cats did not produce rhythmical discharges. However, in one similar monkey experiment 0.4 gm. of the drug given intravenously was followed by a strychnine-like rhythmical discharge from the cerebellar electrodes at a rate of 17 per second, at 100 μv. lasting several minutes (Fig. 19).

*Electrical stimulation.* In 3 of 5 experiments on cats strychnine-like rhythmical discharge was induced by electrical stimulation of the cerebellum.

In the first experiment (C 170) an isolated encephalon was made at the

intercollicular level. No strychnine or any other drug was given. Stimulation was made by contact with phonograph needle electrodes whose points were inserted through intact bone touching the cerebral and cerebellar cortices. A 10 volt 60 cycle current was passed between electrodes in the left cruciate gyrus and right posterior cerebellar lobe for 10 seconds. Immediately following stimulation the two cerebral channels were isoelectric, while the 4 cerebellar channels showed medium amplitude spikes averaging 140–160 μv. at 8–9 per second. Ten seconds later, these spikes were replaced by uniform rhythmical sharp

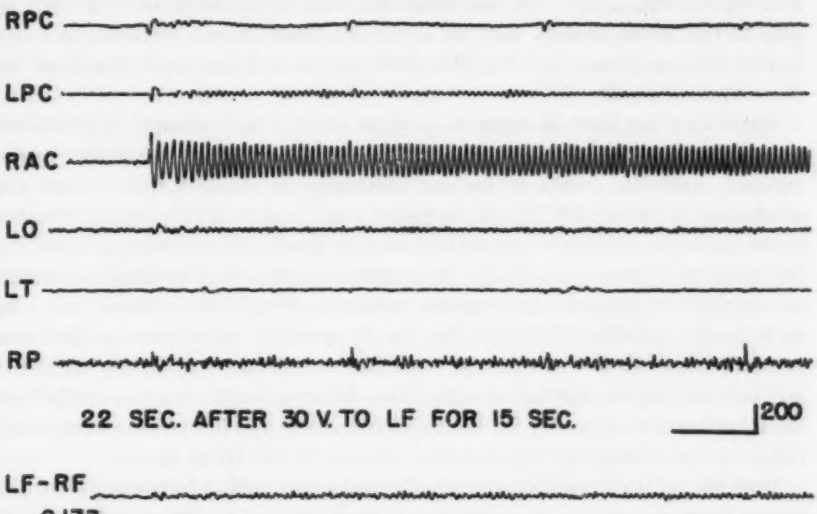


FIG. 20. (C 173) Electrocerebellogram of curarized cat 10 seconds after stimulation of left cruciate gyrus (30 volts, 60 cycles) for 15 seconds. The onset of rhythmical waves is delayed. Duration of rhythmical activity was 16 seconds. Note that the activity appears from the anterior cerebellar lobe while the posterior lobes are isoelectric. Similar phenomena have been produced in "encéphale isolé" preparations by applying the stimulus to the cerebellar cortex.

waves of 120–140 μv. at 19–20 per second lasting for 1–2 seconds in all cerebellar channels.

In another experiment (C 173) using an intact cat, electrical stimulation (30 volts at 60 cycles) of the left cruciate gyrus for 15 seconds was followed in 20 seconds by the sudden onset of large regular sharp waves averaging 200–240 μv. at 14 per second from the right anterior cerebellar lobe lasting for 25 seconds (Fig. 20). During this period the posterior cerebellar, left medial and posterior suprasylvian gyri remained isolectric while the tracing from the right ectosylvian gyrus was much as before stimulation. The character of the cere-

bellar waves produced by electrical excitation was quite similar to that produced by strychnine.

## DISCUSSION

The intrinsic electrical activity of the cerebellum as recorded by the oscilloscope according to Adrian (1) is characterized by very low voltages at frequencies ranging between 150 and 250 per second. Dow (6) described the spontaneous cerebellar potentials as constantly averaging 10 $\mu$v. at frequencies of from 150–250 per second punctuated by bursts of larger waves. This type of activity continued after all cerebellar neuronal connections were divided so long as the blood pressure was not decreased. Spontaneous cerebellar activity having frequencies as high as 1000–2000 per second has been described by Swank and Brendler (13).

Strychnine has been thought to produce little, if any, change in cerebellar potentials. Miller (10) in 1920 applied pledgets of 1% strychnine nitrate to the exposed cerebellar cortex of the cat. Although he did not record from the cerebellum in these experiments, he noted a succession of fine, regular tremors in the ipsilateral hind limb when the knee was flexed. The tremors persisted for indefinite periods and could also be elicited by mechanical or faradic stimulation of the foot pad or by tapping the patellar tendon. Miller believed this to be an entirely cerebellar effect and not due to spread of strychnine to the brain stem. In some of our experiments, when the animal was very lightly curarized and high amplitude rhythmical waves were being recorded from the cerebellum after local injection of strychnine, rapid tremors of the hind limbs were sometimes seen at a frequency approaching that of the electrical waves.

Dow (6) in 1938 recorded large rhythmical waves with a frequency of 70 per second from the cerebellum after topical application of 1:1000 strychnine, but this frequency is at least twice that we observed. Curtis (5) in 1940 noted an increased amplitude of cerebellar potentials after topical application of 0.3% picrotoxin but did not mention the use of strychnine.

It has been generally believed that strychnine does not produce spikes in the cerebellar cortex but the recent work of Moruzzi, Brookhart and Snider (11) and Brookhart, Moruzzi and Snider (4) showed that the cerebellar cortex is capable of producing spikes after topical application of strychnine. In their experiments, 12.5 $\mu$. monopolar alloy electrodes were used to record from the cerebellar cortex at desired depths. With this method they obtained spikes of 0.5–1.0 m. sec. duration and approaching 200 $\mu$v., occasionally as great as 500 $\mu$v. The origin of these potentials was believed to be in the vicinity of the Purkinje cell or granular cell layer.

Snider and Eldred (12) believed that the Purkinje cells and possibly the basket cells were responsible for the intrinsic fast activity of the cerebellum. They considered that one of two reverberating circuits might be responsible for

the phenomenon, one comprising Purkinje cell to central cerebellar nuclei to Purkinje cell; the second, elements of the Purkinje cell layer. The first circuit seemed unlikely since destruction of the cerebellar nuclei did not abolish the activity. Data on the second circuit were not available for the Purkinje cells could not be destroyed selectively.

The rhythmical activity described here would appear to be due to brainstem-cerebellar mechanisms, the precise anatomical channels of which are not known. Since there were no significant alterations from the cerebral cortex during typical rhythmical discharges in the electrocerebellogram, and since section of the brainstem at the intercollicular level did not abolish the characteristic waves, it is apparent that the phenomenon does not depend upon connections with centers above this level (9). Furthermore, since the spinal cord could be divided as high as the first cervical segment without abolishing the rhythmical waves recorded from the surface of the cerebellum it would seem that the spinal medulla is not essential in the mechanism.

Thus it appears that the regions mainly concerned in this response are the cerebellum, medulla oblongata, pons and caudal portions of the mesencephalon. Ablation of the cerebellum did not abolish the rhythmical waves in the medulla and pons, although the waves were not altogether characteristic of those recorded from the intact cerebellum. This might suggest that the cerebellum itself was not a primary part of the mechanism. Yet there is some evidence that the cerebellum is integrally associated with the mechanism responsible for this phenomenon. In the animals which were fed DDT, which is known to cause destruction of the cerebellar nuclei and Purkinje cells (7), the rhythmical discharges could not be produced by injection of strychnine into the cerebellum itself, nor if strychnine were given intravenously.

In other experiments where strychnine was injected into the cerebellum of non-curarized cats in which mid-thoracic cordotomy had been done several days previously, regular pawing movements in the upper limbs appeared within a few seconds, while the lower limbs showed this only after many minutes had elapsed. This would suggest the movements in the upper limbs were due to strychnine stimulation over pathways from the cerebellum or brainstem, while the movements in the hind limbs were the result of systemic absorption of the drug by the distal spinal cord segment.

Attempts to isolate parts or all of the cerebellum by cutting one or more cerebellar peduncles during strychnine discharges have been followed by immediate interruption of the activity. After complete removal of the cerebellum, rhythmical waves have been obtained from the brainstem but in such cases the waves were not so uniform, so great in voltage or so persistent as those obtained with the cerebellum intact.

These observations lend support to the theory that the cerebellum plays an

important role in the basic mechanism of the strychnine rhythmical discharges described in this paper.

It is interesting that apparently identical phenomena are seen in the spinal cord. Bremer (2) has studied the spinal activity following topical application or systemic administration of strychnine. He described the regular occurrence of rhythmical high amplitude waves with a frequency of 10–30 per second. Bremer believed that the waves originated in the anterior column cells and he regarded the phenomenon as an expression of "rhythmical tetanic synchronization" of neuronal aggregates (2). Neurones of the posterior columns are not essential to this activity, Bremer stated, and the onset of strychnine tetany requires the saturation of cellular elements to "le point de départ de la fusée tétanique" (3).

The results of our experiments seem to indicate that the posterior column cells do play a part in the mechanism of strychnine tetany, since it was possible to interrupt or initiate the rhythmical activity by afferent stimuli. This suggests the possibility of a reticular internuncial system as the basis of the synchronous discharge, and a system which probably is continued rostrally from the spinal cord into the brainstem (9). This would explain the independency of the separate regions or the ability of each region to continue firing when anatomically isolated.

That the activity of the cerebral cortex appears relatively little affected by the occurrence of such marked brainstem-cerebellar activity is interesting, but in some instances cerebral cortical activity decreased during cerebellar discharges. Conversely, if such convulsant agents as penicillin are applied to the cerebral cortex before strychnine is injected into the cerebellum, then in most cases the rhythmical discharges from the lower centers do not develop. This suggests a mutually antagonistic relationship between the cerebral and brainstem-cerebellar activity.

## SUMMARY

An unusual type of electrical activity has been described in the electrorhombencephalogram of the cat and the monkey. This is characterized by regular rhythmical waves of high amplitude (200–450 $\mu$v.) at frequencies of 10–32 per second, lasting from several minutes to one hour. Activity of this type has been observed following topical, intravenous or local injection of strychnine, intravenous injection of nitrogen mustard and of dichloro-diphenyltrichloro-ethane (DDT), and electrical stimulation of the cerebellum.

Wave forms of this type were recorded from the cerebellar cortex, dentate nuclei, brainstem and spinal cord.

The physiological mechanisms which may be responsible for this phenomenon are discussed. The possibility of a reticular internuncial system common

to cerebellum, brainstem and spinal cord as the basis for this type of activity is suggested.

The characteristics of the normal electrocerebellogram of the cat are given, as well as the effects of metrazol, picrotoxin, caffeine, coramine, eserine, acetylcholine, pentobarbital, tolserol, procaine, penicillin and streptomycin, administered locally, intravenously or topically.

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# STRUCTURE OF THE NUCLEOLUS AS REVEALED BY THE ELECTRON MICROSCOPE*

## A Preliminary Report

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The nucleolus has usually been described as a homogeneous, structureless mass in which a variety of granules and vacuoles may be embedded (1, 2, 3). The high magnification attained by the electron microscope has made it possible to observe complex structure within the nucleoli of a number of normal and pathological tissues. The recognition of a well-defined nucleolar structure presents new aspects for the study of the function of this poorly understood body.

### MATERIALS AND METHODS

The following types of tissues were fixed in 2 per cent osmic acid by immersion for periods ranging from 10 minutes to about 15 hours:

A. Chorio-allantoic membranes of normal and pseudorabies virus infected 12, 13 and 14 day old chick embryos.

B. Biopsy specimens of normal human skin and human skin infected with chicken pox.

C. Biopsy specimens of normal human liver and liver from a patient with obstructive jaundice.

D. Normal mouse liver and liver from a mouse suffering from a disease resembling viral hepatitis (4). These tissues were obtained through the courtesy of Dr. J. Jordan.

E. Tissue cultures of the following malignant cells grown in roller tubes: (a) rat sarcoma (T-333) (5); (b) human chondromyxosarcoma (DlRe) (6); (c) human malignant cartilage cells (7). These tissue culture cells were furnished through the courtesy of Dr. G. O. Gey.

Chick chorio-allantoic membranes were also studied after fixation in 10 per cent buffered neutral formalin for one hour. After fixation, all tissues were washed in running tap water for several hours and dehydrated by transfer through a series of alcohols. They were then embedded in methacrylate and sectioned by means of the techniques developed at the National Bureau of Standards (8).

### OBSERVATIONS

Although many nucleoli conformed to the usual morphological concept of homogeneous, roughly spherical masses (Fig. 1), a large number showed a complex internal structure, usually consisting of a tangled mass of branching or anastomosing filaments (Figs. 3, 4). The filaments were approximately 0.1 micron in width but varied in this dimension both within a single filament and between neighboring filaments. Occasionally, the filaments were loosely em-

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bedded in an amorphous matrix combining the features of both types of nucleolar structure (Fig. 2). The nucleoli appeared to be in intimate contact with the surrounding nucleoplasm since there was no evidence of a nucleolar membrane in any of the sections. In the chick chorio-allantoic membrane, the nucleolar structure was apparent with both the osmium and formalin fixatives (Fig. 5). Fixation time in osmic acid did not affect the nucleolus appreciably, the filaments appearing as clearly in cells fixed for ten minutes as they did in those fixed for about fifteen hours. The structure was not confined to any particular cell type, but was present in most of the cells comprising the tissues. An exception to this was found in the nuclei of chick blood cells, which had a nuclear morphology entirely different from that of the other cells in the chorio-allantoic membrane.

Evidence that the nucleolar structure observed was not an artifact of fixation was obtained by studying living DlRe cells in the phase contrast microscope.[1] The nucleoli in many of the living cells were approximately the same size and shape and showed the same filamentous internal structure as those seen in the sectioned material (Fig. 6). The remarkable similarity of the phase contrast and electron microscope images of this cell line demonstrates not only that the nucleolar structure seen in fixed cells faithfully represents the structure present in living cells, but also shows that osmic acid can be used to advantage in studying nuclear morphology.

## DISCUSSION

The occurrence of nucleolar structure in the wide variety of vertebrate cells and tissues which were examined suggests that, with a few exceptions, it may be expected to be found in all vertebrate cells. The fact that it was observed in normal as well as pathological tissues indicates that it is a normal morphological feature of the cells. The simultaneous presence, in similar cells of a tissue, of homogeneous nucleoli and nucleoli with filamentous structure, as well as the occasional appearance of nucleoli which combine both features, suggests that a transformation from a homogeneous mass to a complex filamentous tangle, or the reverse, may occur within the nucleolus in the course of its functional cycle (9).

## SUMMARY

In addition to homogeneous, structureless nucleoli, nucleoli possessing a characteristic filamentous structure were observed in sections of eleven different normal and pathological tissues. Comparison with the appearance of nucleoli in living cells gave evidence that the structure observed in the sectioned ma-

[1] We are indebted to Petras Sapranauskas and to Dr. George Gey for their invaluable assistance in this phase of the work.

terial was not an artifact of fixation. No evidence of a nucleolar membrane was found in any of the preparations.

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While this manuscript was in preparation the authors were shown pictures of sections of several tissues by Dr. K. R. Porter and Dr. G. E. Palade, of the Rockefeller Institute for Medical Research, in which the nucleoli contained structures similar to those reported here.

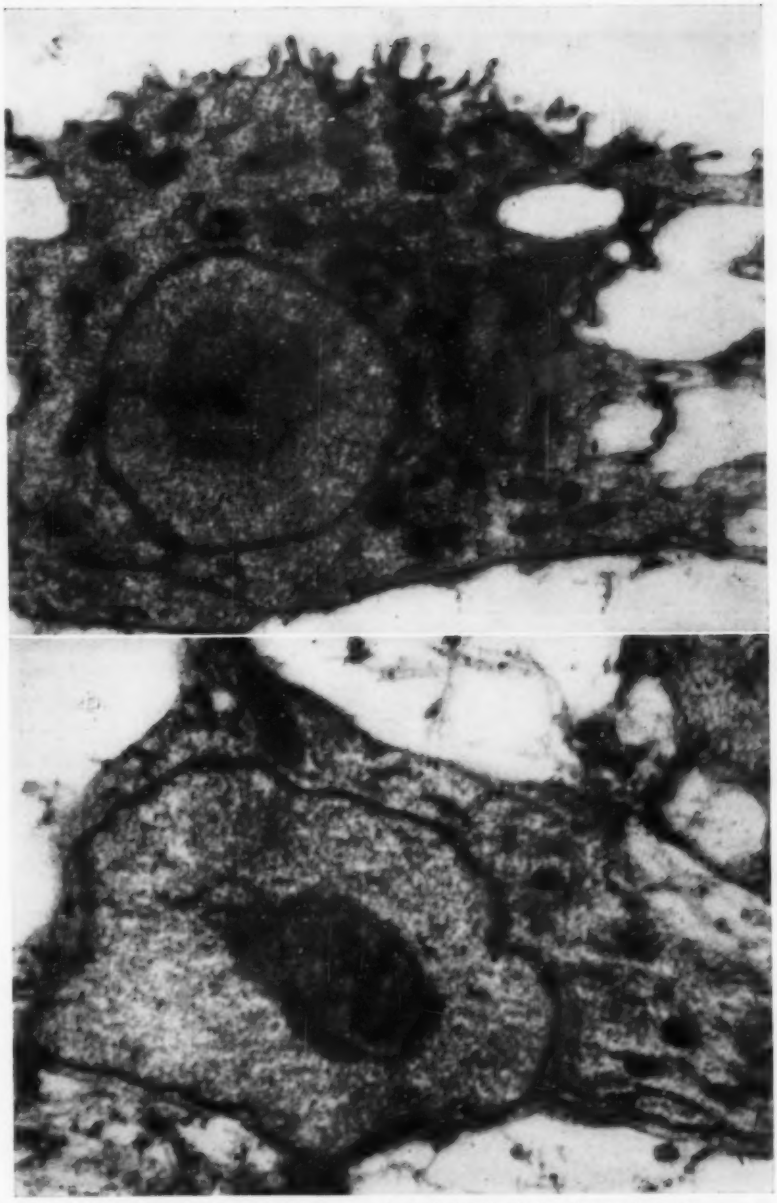


FIG. 1. Homogeneous nucleolus in an endothelial cell of the chorio-allantoic membrane of a 12 day old chick embryo. Fixation—15 hours in osmic acid. ×14,400.

FIG. 2. Nucleolus composed of filaments in a homogeneous matrix in a fibroblast of the chorio-allantoic membrane of a 13 day old chick embryo. Fixation—15 hours in osmic acid. ×14,400.

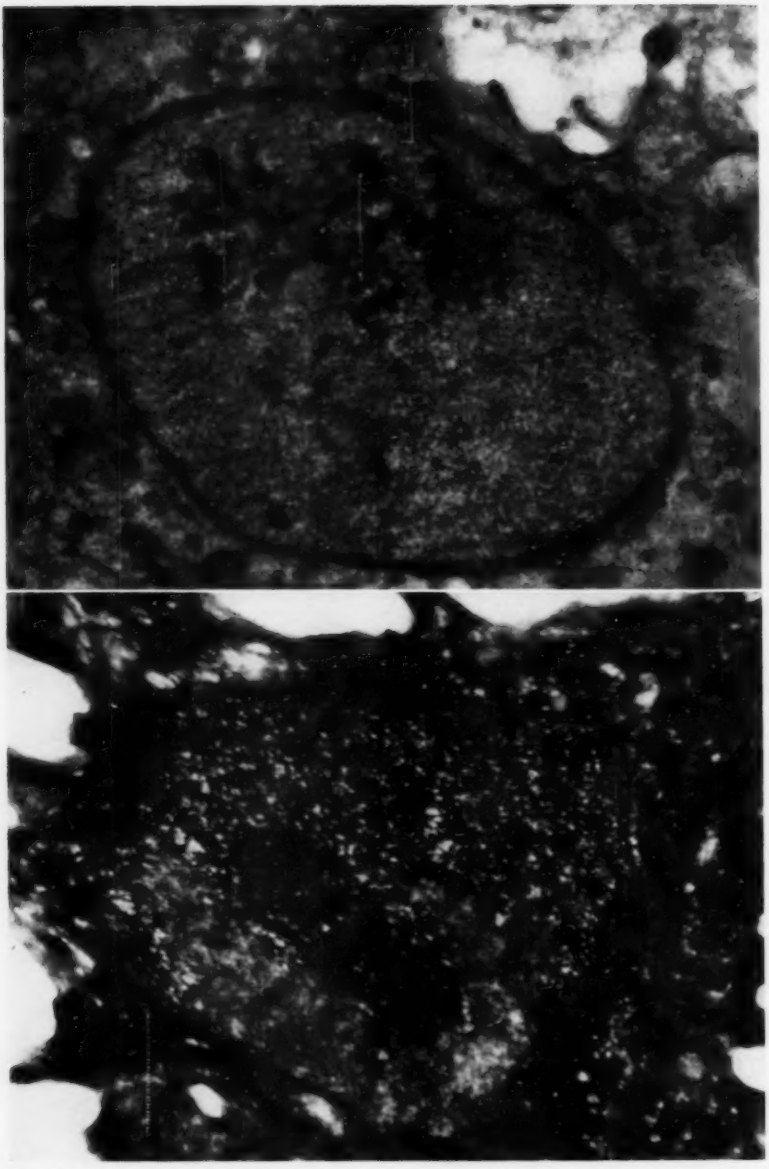


FIG. 3. Filamentous nucleolar structure in a cultured human malignant cartilage cell. Fixation—2 hours in osmic acid. ×14,400.

FIG. 4. Filamentous nucleolar structure in a specimen of human skin taken from a chicken pox patient. Fixation—2 hours in osmic acid. ×14,400.

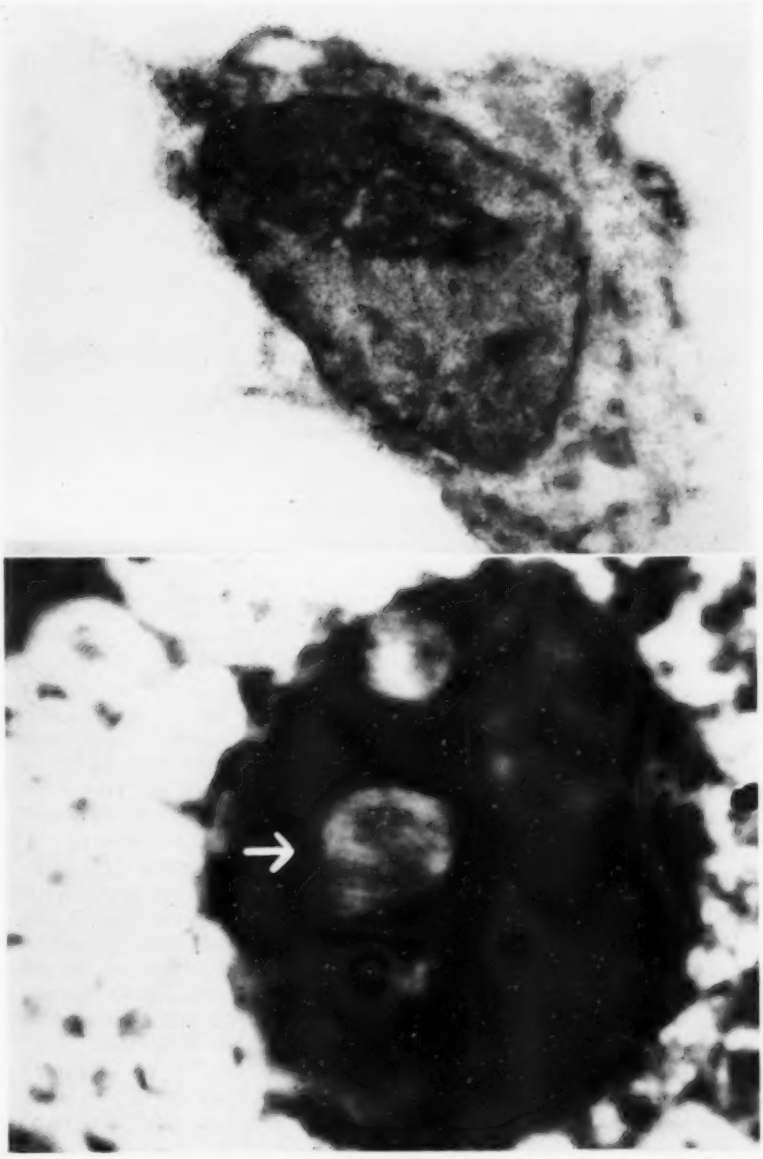
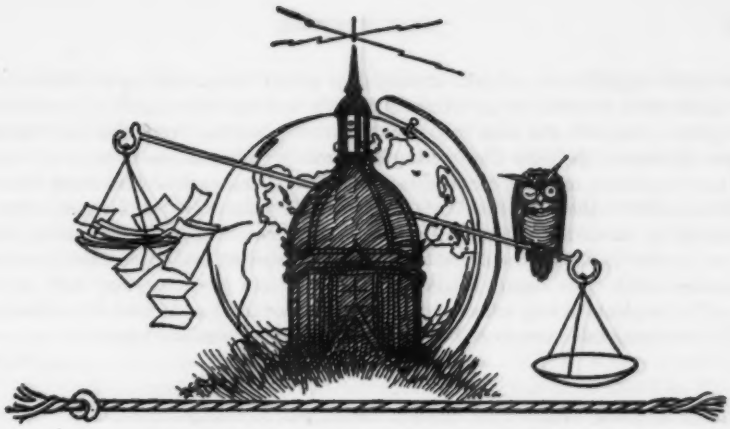


FIG. 5. Filamentous nucleolar structure in a fibroblast of the chorio-allantoic membrane of a 12 day old chick embryo infected with the virus of pseudorabies. Fixation—1 hour in neutral formalin. ×14,400.

FIG. 6. Phase contrast photomicrograph of a nucleolus in a living DlRe cell. ×6,000.



# BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

**Selected Writings of Sir William Osler. 12 July 1849–29 December 1919.** With an Introduction by G. L. KEYNES. 278 pp., $4.00. *Oxford University Press, New York.*

Physicians will recognize the preparation of this book as an important service by a committee of the Osler Club of London. Alfred W. Franklin carried an important part of the editorial burden for the Club and was fortunate in having the assistance of W. W. Francis of the Osler Library at McGill University. G. L. Keynes contributed an introduction to this excellent selection of Osler's non-scientific essays—historical, philosophical and dealing with education. In date of preparation, the essays range from the *Letters To My House Physicians* (1890) to *The Old Humanities and the New Science* (1919), in content, from *A Way of Life* to *Illustrations of the Bookworm*; the interesting illustration from the latter essay is one of several in the book.

The Club has succeeded in its aim of giving "the medical student a taste of Osler". The great majority of this new volume's 16 essays are not included in the heretofore most readily available nibble of his selected writings, *Aequanimitas*. Hence there is that to be tasted in the new collection which is also of relish to established members of the medical profession as well as students. Osler, a man of great breadth of general learning, trained in a scientific discipline, has much to say to all physicians in his dynamic, readable style.

Thus, in these days of international and social turmoil, one is interested in his reactions to the troubled days of World War I, recorded in the essay of 1919. And, as regards personal philosophy for the "voyage of life," we find in the volume the essay *A Way of Life*, with its suggestion of " 'day-tight compartments' as the most certain way to ensure safety." Those seeking information on the interesting subject of Osler's attitude toward religion can attempt to make tentative conclusions, as has this reviewer. A background of great knowledge of the Bible, revealed by his frequent quotations, and a closing paragraph or two in *A Way of Life*, both suggest that Osler had religious convictions which he was careful, to the point of being enigmatical, not to impart brusquely to a possibly sceptical reader. The

same veiled suggestion of religious conviction is gained from a reading of Osler's *Science and Immortality*, an essay which weighs a difficult problem from a viewpoint which is as appropriate today as it was when it was written in 1904; one may regret that the limitations of space prevented the Osler Club's committee from including the essay in this volume.

There is another, most important category of the medical profession to which this book should be offered—the *premedical* student. One of its essays, *A Way of Life*, was addressed specifically to an undergraduate group. Further, he who waits until his medical school days to develop in himself the characteristics of temperament and the familiarity with the humanities which Osler rightly proclaimed important to a physician, may wait too long. Premedical students in high school and in college cannot but benefit from this collection of essays portraying the interests and wisdom of a great physician and teacher.

P. H. F.

**Metabolic Methods.** Clinical Procedures in the Study of Metabolic Functions. By C. Frank Consolazio, Robert E. Johnson, and Evelyn Marek. 471 pp., $6.75. *The C. V. Mosby Co., St. Louis, Missouri.*

Several decades ago, when he pointed out that Aristotle retarded science a thousand years by insisting "Classify" when he should have said "Measure," A. N. Whitehead justified cook books. *Metabolic Methods* is a cook book—and in no derogatory sense. Compiled by workers experienced in training technicians and in performing multiple analyses on large numbers of samples of biological material, it offers carefully detailed recipes for biochemical and physiological procedures. All of these procedures are those the authors have used and have found satisfactory for their needs, which have required them to aim for simplicity and rapidity even if this, at times, meant sacrifice of specificity and accuracy. There are references, not always complete, to other methods, but the real advantage of the book lies in the elementary presentation of workable techniques, complete with stock list, example, calculation of results, and precautions. It is certainly the next best thing to observing a skilled technician in motion. The diagrams of apparatus are simple, yet detailed enough to permit local manufacture and assembly.

The variety of methods treated in this book is vast: chemical analysis of electrolytes, of proteins and nitrogen compounds, of carbohydrates and derivatives, and of fats and derivatives, vitamin and hormone assay, assessment of commonly tested enzyme systems, determination of pigments, measurement of pH, microbiological procedures, pulmonary function assessment, measurement of body fluid spaces, and even clinical laboratory procedures.

It is extremely useful to have all this information available in one volume. There is, of course, too much compression for first-rate scholarship, but that is not the purpose of this book. However, even within the framework elected by the authors there will be disagreement. Thus, the reviewer prefers: for blood glucose, the Nelson arsenomolybdate method rather than the Folin-Malmros Prussian blue method; for lactic acid, the Barker-Summerson colorimetric method rather than Edwards' iodometric method; for creatine, any of several modifications of the original Folin-Wu method; for amino acids, the ninhydrin methods rather than the old Folin method; for magnesium, the Titan yellow method rather than the magnesium ammonium phosphate method; and internal standard flame photometry rather than direct comparison flame photometry. Nor will many workers want to measure cardiac output by the acetylene method.

Despite the remarkable condensation in this volume there remain essentially extraneous portions. Much of the section on instrumentation is superfluous; for example, there are 12 pages concerning the Beckman Model DU spectrophotometer which appear not dissimilar

to the manufacturer's information supplied with the instrument. An excellent idea was the frequent use of D'Ocagne alignment charts throughout the book. Unfortunately, the pages don't lie flat and the charts can't be used conveniently, a condition that could have been remedied by use of a ring or spiral binding or by perforating the charts to permit tearing them from the book.

None of these criticisms negates the widespread usefulness of this reasonably-priced book. It is recommended without further caveat to those with experience in related techniques who need to know or recall exactly how to carry out a given procedure.

K. L. Z.

**Proceedings of the Forum Sessions; Thirty-Sixth Clinical Congress of the American College of Surgeons, Boston, Massachusetts, October, 1950.** Surgical Forum Committee, Owen H. Wangensteen, Warren H. Cole, Robert E. Gross, Michael L. Mason, Carl A. Moyer, and I. S. Ravdin. 665 pp., $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

This volume represents the first publication, as a whole, of the papers presented at a Forum on Fundamental Surgical Problems at the Clinical Congress of the American College of Surgeons. The papers given at the Forum Sessions are almost entirely reports of an experimental nature. The 1950 Forum consisted of over 200 presentations covering a wide variety of material. For publication in this volume each author has produced a concise article of less than 3000 words. These brief, compact reports are in general clearly written, factual, and meaty with minimum verbiage. For editorial reasons some of the papers had to be presented in abstract form.

This is an extremely valuable collection of reports on current research in surgery and represents a formidable amount of investigative work. It is essential reading for those engaged in surgical research. The Surgical Forum Committee, the publishers, and the contributors have all done a good job.

H. W. S., Jr.

**Anatomy in Surgery.** By Philip Thorek. 970 pp., $22.50. *J. B. Lippincott Co., Philadelphia, Pa.*

Dr. Thorek has made a considered, scholarly effort to provide a text which will bridge the wide chasm between basic anatomy as taught to the beginning medical student and the regional anatomy which is the keystone of operative surgical technique. Firm adherence to what the author has termed "a simple method of presentation and correlation," supplemented by a profusion of excellent and refreshingly original semi-diagrammatic drawings has resulted in a notable addition to the catalogue of surgical references.

The body is divided into ten regions and each independently treated. In each region subdivisions are made and the "presentation" of the basic anatomy with nerve and blood supply follows a brief review of the embryology of the region. The "correlation" with surgical considerations is then made with a facility which leaves no awkward hurdle interposed. The discussions of surgical lesions and procedures are concise and always illustrative of the anatomical detail under consideration. The author carefully avoids the pitfall of losing continuity in a welter of clinical data which is not strictly to the point.

The text is satisfactorily abreast of recent additions to anatomic knowledge, particularly with regard to the intra-thoracic region. The discussion of the segmental anatomy of the lungs, and the description of the heart and great vessels are both well-handled with illustrative examples of recent surgical advances. (One is surprised to note, however, that a short

section on "Surgery of the Aorta" implies through omission that aortic resection is not yet part of the surgical armamentarium.) In the discussion of the liver, a description of splenorenal and porto-caval shunts is skil"fully employed to clarify the anatomical considerations of this area.

The author's clear and direct style of prose is assuredly worthy of a final word of compliment. The readability of the text further insures the value of this fine contribution.

J. C. H.

**Die Trübungsformen der Menschlichen Linse.** By HANS SAUTTER. 139 pp., Ganzleinen DM 49.80. *Georg Thieme Verlag, Stuttgart, Germany.*

The examination of cataracts with the slit lamp corneal microscope has revealed that many different morphologic patterns may be distinguished which are in varying degree characteristic of various etiological factors. The monumental work of Vogt in this field is well known but, as the author points out, Vogt's Atlas is no longer readily available to all students of this subject.

The present volume was designed to make available in condensed form an atlas of illustrations with text covering various forms of cataracts. The illustrations and their reproduction are excellent. The text is brief but informative. The book should be useful to beginners in slit lamp microscopy of the eye.

Too much emphasis can, however, be placed upon the morphologic distinctions of different cataracts. While it is true that the cataracts of diabetes, tetany, scleredema, etc. are generally dissimilar in their morphologic patterns, the pattern for any particular type varies over a fairly wide range so that etiologic diagnosis cannot with certainty be based solely on the observed pattern. The student needs to keep these reservations in mind while he pursues with enthusiasm the diagnostic suggestions that arise out of the morphologic findings.

J. S. F.

**A Text-Book of X-ray Diagnosis,** 2nd edition. Vol. 2. By BRITISH AUTHORS in 4 volumes. Edited by S. Cochrane Shanks and Peter Kerley. 702 pp., $15.00. *W. B. Saunders Co., Philadelphia, Pa.*

Volume II is concerned with the cardiovascular and respiratory systems. Peter Kerley has written the first part concerning the cardiovascular system and the late Edward Wing Twining has written the second part on the respiratory system. This last section was revised by Peter Kerley.

The cardiovascular system is divided into ten chapters devoted to 1) x-ray examination, 2) normal, 3) displacement, 4) enlargement, 5) valvular diseases, 6) congenital heart diseases, 7) aorta, 8) pericardium, 9) pulmonary vessels, 10) peripheral vessels.

The respiratory system is divided into 24 chapters consisting of eight chapters covering the normal anatomy of the thorax and contents. The remaining chapters are devoted to diseases of the chest in the following order: chapter 19—diseases of the bronchi, 20—atelectasis, 21—emphysema, 22—pneumonias, 23—lung abscess, 24—dust diseases, 25—fungi, protozoa, and parasites, chapters 26 to 29—tuberculosis, 30—mediastinal disease, 31—primary neoplasia, 32—metastatic neoplasia, 33—pleurisy, 34—tumors and calcification of the pleura, 35—pneumothorax, and 36—post-operative appearance of the chest.

In general the new edition has been greatly expanded, revised and modernized compared with the old edition published in 1938. A rough estimation of the expansion can be gained by comparing the 491 pages of the old edition and the 328 illustrations of the old edition with the 702 pages in the new edition and the 605 illustrations.

Specifically in the first part dealing with the heart and great vessels new paragraphs have been added in angiocardiography, electrokymography, and funnel chests. Minor modifications are noted in kymography, cineradiography, and kyphosis. Considerable expansion has been made on paragraphs dealing with displacement due to pulmonary diseases and alteration in the position of the diaphragms.

The chapter on cardiac enlargement has been extensively revised. Some newer concepts such as the analysis of the inflow and outflow tracts as put forth by Professor E. Zedansky of Vienna are incorporated. The chapter on valvular diseases of the heart has also been extensively revised. As would be suspected the entire chapter on congenital heart disease has been modernized and greatly expanded in keeping with the recent developments. The chapter dealing with the aorta has been somewhat expanded but the chapters on the pericardium and pulmonary vessels have been completely rewritten and improved greatly.

Regarding the respiratory diseases the chapters dealing with roentgen methods and anatomy have in general been slightly revised. The one exception is the anatomy of the bronchi and bronchopulmonary segments which have been revised in accordance with the researches of Foster-Carter and Hoyle.

Several paragraphs have been added to the congenital abnormalities of the lungs and bronchiectasis, atelectasis, and emphysema. The chapter on cystic disease has been much better defined and elaborated upon according to modern views. Dr. Kerley has put in a valuable chapter on lung allergies and trauma together with the older chapter on pneumonias.

The chapter on occupational and dust diseases of the lung has been extensively revised as well as the chapter on spirochetal, fungous, protozoan and parasitic infections. On tuberculosis the author has kept the excellent old text practically intact, although he does discuss the role of atelectasis and tuberculosis and also the adult primary complex. The discussion on sarcoid is entirely new. In primary neoplastic diseases he has added paragraphs on obstructive emphysema and alveolar cell carcinoma or pulmonary adenomatosis. The chapter dealing with pleurisy discusses dry pleurisy in much greater length and also includes the Meig's syndrome.

In general the new edition has been greatly improved and expanded and modernized. It is a worthy successor of the old edition which has been a standard classic roentgenologic text. This edition is recommended as a reference and study book to medical libraries, radiologists, chest physicians, and students of roentgenology. The one flaw according to the consensus of American opinion is that the reproductions of roentgenograms are printed as positives rather than the original negative tonal scale.

D. G.

**Hospitals—Integrated Design,** 2nd edition. By ISADORE ROSENFIELD. 398 pp., $15.00. *Reinhold Publishing Corp., New York.*

This revised edition is the best attempt to date to provide the builders, planners and students of hospitals with the most current published data on hospital building planning. The author makes provision for suitable historical background in hospital building planning and development.

The discussion of architectural problems is good. The book may serve as a usable guide to hospital architecture. There are many details of design. The book also covers presentation of the problem for the trustee, doctor, hospital administrator—the planners of hospitals.

Economy of construction is emphasized, especially in the patient areas. Acceptance of these ideas will be primarily dependent on the patient's reception to these designs.

L. F. G.

## BOOKS RECEIVED FOR REVIEW

**Causalgia.** By FRANK H. MAYFIELD. 65 pp., $2.25. *Charles C. Thomas, Springfield, Illinois.*

**Chronology of Ophthalmic Development.** American Lecture Series. By ARTHUR H. KEENEY. 22 pp., $2.00. *Charles C. Thomas, Springfield, Illinois.*

**The Collected Papers of Adolf Meyer.** Four Volume Set $30.00. Edited by EUNICE WINTERS. Vol. III, Medical Teaching. With an Introduction by FRANKLIN G. EBAUGH. 577 pp. *The Johns Hopkins Press, Baltimore, Md.*

**German-English, English-German Dictionary for Physicians in 2 volumes.** Vol. 1. By FRITZ LEJEUNE. 1352 pp., Ganzleinen DM 24. *Georg Thieme Verlag, Stuttgart, Germany.*

**Human Biochemistry, 3rd edition.** By ISRAEL S. KLEINER. 695 pp., $7.00. *The C. V. Mosby Co., St. Louis, Missouri.*

**Leibesübungen mit Körperbeschädigten.** By HANS LORENZEN. 218 pp., kart. DM 7.50. *Georg Thieme Verlag, Stuttgart, Germany.*

**Simplified Nursing, 5th edition.** By FLORENCE DAKIN AND ELLA M. THOMPSON. 730 pp., $4.00. *J. B. Lippincott Co., Philadelphia, Pa.*

**Studies of Undernutrition, Suppertal 1946–9.** By MEMBERS OF THE DEPARTMENT OF EXPERIMENTAL MEDICINE, CAMBRIDGE, AND ASSOCIATED WORKERS. Privy Council Medical Research Council Special Report Series No. 275. 404 pp., 12s. 6d. net. *His Majesty's Stationery Office, London, England.*

**Tobacco and the Cardiovascular System.** By GRACE M. ROTH. 66 pp., $2.25. *Charles C Thomas, Springfield, Illinois.*

**Verletzungen der Lungen und des Brustkorbes.** By W. STEFFENS. 320 pp., kart. DM 10.90. *Georg Thieme Verlag, Stuttgart, Germany.*

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